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The undesirable effects of neuromuscular blocking drugs

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Summary

Neuromuscular blocking drugs are designed to bind to the nicotinic receptor at the neuromuscular junction. However, they also interact with other acetylcholine receptors in the body. Binding to these receptors causes adverse effects that vary with the specificity for the cholinergic receptor in question. Moreover, all neuromuscular blocking drugs may cause hypersensitivity reactions. Often the symptoms are mild and self-limiting but massive histamine release can cause systematic reactions with circulatory and respiratory symptoms and signs. At the end of anaesthesia, no residual effect of a neuromuscular blocking drug should be present. However, the huge variability in response to neuromuscular blocking drugs makes it impossible to predict which patient will suffer postoperative residual curarization. This article discusses the undesirable effects of the currently available neuromuscular blocking drugs including the definitions, diagnosis and causes of hypersensitivity reactions and postoperative residual curarisation.

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Before Griffith and Johnson [1] introduced curare in 1942, muscle relaxation was produced by attaining deep planes of anaesthesia, with the concomitant risks of cardiovascular and respiratory depression. The introduction of neuromuscular blocking drugs (NMBs) made 'balanced anaesthesia' possible and revolutionised the practice of anaesthesia. However, it soon became obvious that NMBs had both disadvantages and adverse effects. An adverse effect (or adverse drug reaction) is defined by the World Health Organisation as 'a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function'. Neuromuscular blocking drugs are designed to bind to the nicotinic receptor at the neuromuscular junction. However, they also interact with other acetylcholine receptors such as the nicotinic receptors in autonomic ganglia and the carotid body chemoreceptors, as well as the muscarinic receptors of the heart. Binding to these receptors results in adverse effects that vary with the potency and specificity for the cholinergic receptor in question. This article focuses on the adverse effects of the currently available NMBs, including postoperative residual curarisation (PORC) and hypersensitivity reactions. The influences of age, temperature, pH, electrolyte concentrations, and hepatic and renal failure on the effects of NMBs cannot be considered as adverse reactions and are not discussed. The adverse effects of older drugs and interactions between NMBs and other drugs are also outside the scope of this review.

Hypersensitivity reactions to neuromuscular blocking drugs

Background and epidemiology

Hypersensitivity reactions to NMBs have been reported sporadically in the literature since the 1950s. Initial case reports related hypersensitivity reactions to single agents used at the time, such as curare or suxamethonium [2]. The introduction of new NMBs was followed by a transient increase in case reports of hypersensitivity reactions to gallamine, alcuronium and pancuronium in the 1970s, atracurium and vecuronium in the 1980s, and rocuronium, mivacurium and cisatracurium in the 1990s, largely reflecting increased vigilance during the introduc-

tion of new drugs and their relative market shares. Not surprisingly, a similar trend was noted in a study of reports of adverse drug reactions to NMBs in the UK between 1967 and 2000 [3].

The use of NMBs is almost exclusively confined to general anaesthesia, and larger studies of hypersensitivity reactions to NMBs are thus mainly found in the literature on hypersensitivity reactions during anaesthesia. Systematic investigations of such reactions were initiated in the late 1970s in anaesthesia allergy centres in the UK, Australia and France, and a standardised investigation procedure was agreed in Nancy in 1983 [4] based on a detailed clinical history, blood tests (IgE levels and histamine release) and skin-testing (skin prick test and intradermal test), which still provide the basis for the investigational programmes used today.

Definitions

Many different terms such as anaphylactic, anaphylactoid, pseudo-allergic and histaminoid have been used in the literature, reflecting differences in definition and in underlying mechanisms. Attempts at standardising definitions of hypersensitivity reactions have been made [5] and according to the new definitions the overall term *hypersensitivity reaction* should be used. Hypersensitivity reactions can be divided into allergic and non-allergic hypersensitivity reactions, and the allergic hypersensitivity reactions can be further divided into IgE-mediated and non-IgE-mediated reactions. Anaphylaxis is used as an overall term for severe, generalised and life-threatening reactions, and divides into the same categories as mentioned above. To avoid confusing terminology the term *hypersensitivity reaction* is used in this article.

Incidence

Hypersensitivity reactions during anaesthesia are rare but the true incidence is difficult to estimate due to factors such as under-diagnosis, under-reporting and differences in investigations and definition. The estimated incidence of hypersensitivity reactions during anaesthesia based on referrals to anaesthesia allergy centres ranges between 1 : 1250 anaesthetics and 1 : 13 000 anaesthetics [6]. A prospective study of suspected hypersensitivity reactions in a single hospital over a 2-year period produced an incidence of IgE-mediated hypersensitivity reactions of 1 : 3180 anaesthetics [7].

Mechanisms and clinical signs

It is often not possible to determine the mechanism behind hypersensitivity reactions in the clinical setting. Most NMBs are known to cause non-specific histamine release from mast cells (benzylisoquinolines are more potent histamine releasers than aminosteroidal NMBs), most of which can be prevented by slow injection or pretreatment with antihistamines [8]. However, symptoms are usually mild and mainly consist of self-limiting flushing. However, massive histamine release can cause systemic reactions with circulatory and respiratory symptoms and signs.

A less common mechanism underlying hypersensitivity reactions is thought to be a high affinity for the M2 muscarinic receptor leading to an augmented parasympathetic response to intubation and airway instrumentation causing severe bronchoconstriction, mediated via the M3 muscarinic receptor [9]. This mechanism is thought to be the cause of cases of severe bronchospasm after the administration of rapacuronium in children [10], leading to withdrawal of the drug from the market in 2001, only 19 months after it was approved for use.

Severe hypersensitivity reactions to NMBs are usually IgE-mediated, with the quaternary ammonium ion as the major allergenic epitope. As NMBs have two quaternary ammonium ion epitopes, they can cause cross-bridging of specific IgE receptors on the surface of mast cells, causing degranulation and IgE-mediated hypersensitivity reactions [11]. Symptoms can range from mild skin symptoms to full blown anaphylaxis with circulatory collapse and severe bronchospasm.

As the quaternary ammonium ion is present in all NMBs there is a risk of cross-sensitisation if the major allergenic epitope is the ammonium ion epitope itself. However, in some cases adjacent parts of the molecule make up the allergenic epitope [12] and other factors such as flexibility of the molecule and the distance between the quaternary ammonium ions determine the allergenicity of the drug and the risk of cross-sensitisation [11]. Reports on the incidence of cross-sensitisation between NMBs in the literature originate mainly from large French surveys that showed a 63.4% incidence of cross-sensitisation between one or more NMBs in patients sensitised to NMBs [13]. A study from Paris of children investigated after hypersensitivity reactions during anaesthesia found cross-sensitisation between NMBs in 23/30 children who tested positive to an NMB based on positive intradermal test results [14]. Interestingly, in 6/18 cases in which the child tested negative to the NMB to which they had been exposed, positive intradermal test results were found for an NMB to which the child had not been exposed. Positive results were seen at the highest intradermal test concentration for NMBs in all but seven cases. The authors concluded that false positive tests could not be ruled out, as there was no control group. A high incidence of cross-sensitisation between NMBs has also been reported from Australia [15], but the authors

concluded that the incidence of cross-sensitisation is highest on serological antibody testing, intermediate with intradermal testing and lowest on skin-prick testing, and that they could not confirm that cross-sensitisation is clinically relevant. There is no doubt that there is a risk of cross-sensitisation with NMBs but the questions is whether this risk has been overestimated in the past. Further studies are needed to explore this in the future.

The quaternary ammonium ion is present in a large number of foods, household chemicals, disinfectants and industrial materials, and it was postulated early on that prior sensitisation to the ammonium ion could be the explanation for reactions on first-time exposure to NMBs [16].

Recently, the striking differences in NMB sensitisation in Norway (high incidence) and Sweden (low incidence) have been highlighted, and a study looking for specific antibodies against morphine and suxamethonium, which carry the quaternary ammonium ion, showed that these antibodies were seen more commonly in Norwegian blood donors and allergic patients [17]. This led to a search for a drug or compound that may have caused this sensitisation. Pholcodine, which is present in cough mixtures marketed widely in Norway but not in Sweden, is now suspected as the potential cause of this sensitisation. Pholcodine is a very potent stimulator of IgE production [18], and preliminary findings indicate that the availability of pholcodine in different countries matches the frequency of hypersensitivity reactions to NMBs [19]. This 'pholcodine hypothesis' is currently under further investigation in a multicentre study [6].

Diagnosis and causes

The diagnosis of hypersensitivity reactions during anaesthesia often represents a challenge because anaesthetic drugs in themselves have adverse circulatory and respiratory effects. However, a good outcome depends on prompt recognition and treatment [20]. All drugs and substances used can potentially cause hypersensitivity reactions during anaesthesia, e.g. opioids, anaesthetics, antibiotics, and even substances like Patent Blue (used for sentinel node mapping) have been incriminated. Latex and chlorhexidine are used in virtually all operations and invasive procedures, and some centres suggest testing for these compounds in all patients referred for investigation after suspected hypersensitivity reactions during anaesthesia [21].

Large studies of pooled results from up to 40 different anaesthesia allergy centres in France were published in the 1990s, consistently showing that NMBs were the leading cause of hypersensitivity reactions during anaesthesia [13]. Interestingly, the proportion of NMBs causing reactions has decreased over the years, from 81% of investigated reactions in the survey ending in 1989 to 54% of investigated reactions in the survey ending in 2002. Reports from Australia [15] and Norway [22] have also shown a high proportion of reactions caused by NMBs. A small study from a single centre in Denmark could not reproduce these findings [21], and a recent small study from a single centre in France [7] found that latex caused 55% of reactions and NMBs only 27% of reactions.

The reasons for the differing results in both frequency of sensitisation and cross-sensitisation to NMBs are likely to be multifactorial, caused by differences in anaesthetic practice and adverse reaction reporting in different countries. More recently, differences in sensitisation based on the exposure to pholcodine in different countries have been implicated.

Another factor may be the practical difficulties of implementing and monitoring standardisation of test methods and diagnostic criteria across multiple centres despite clear and comprehensive guidelines for investigation published by the Société Francaise d'Anesthésie et de Réanimation [23]. Performance of skin testing and interpretation of the results requires experience, and intradermal testing is particularly prone to producing false positive tests [24]. The concentrations used for skin testing have also been debated [25, 26], but a large study from France on 111 volunteers tested for all commercially available NMBs led to only minor modifications of the recommendations. It was suggested that the maximum concentration used for rocuronium, vecuronium and pancuronium be decreased in order to decrease the risk of false positive tests with these compounds. Similarly, it was suggested that the maximum concentration of mivacurium be increased in order to decrease the risk of false negatives with this compound [27].

As a quaternary ammonium ion is present in all NMBs and many other drugs, testing for specific antibodies to the quaternary ammonium ion is a non-specific way to confirm sensitisation to NMBs. The development of IgE analysis specific for the individual compounds may give a more reliable picture of sensitisation, but this is as yet only available for suxamethonium and more recently rocuronium [28].

Hypersensitivity reactions during anaesthesia are rare occurrences that require investigation in specialised centres [20]. Neuromuscular blocking drugs have been incriminated as the leading cause of these reactions but the 'pholcodine hypothesis' has highlighted differences in sensitisation patterns between countries that are under further investigation. Continued centralisation and standardisation of investigation programmes and diagnostic criteria will improve sensitivity and in particular the specificity of existing test methods.

However, it should be kept in mind that a false negative test can create a potentially life-threatening situation for the patient who is exposed to drug for a second time, whereas a false positive test simply restricts the number of available drugs for use, which is not usually a problem.

The focus should be turned away from incriminating single drugs or drug groups and should instead be directed towards improving awareness about the diagnosis and treatment of hypersensitivity reactions. This in turn would decrease the fear of rare hypersensitivity reactions during anaesthesia, which can in turn lead to an inappropriate choice of drugs. The aim should be to use NMBs when they are clinically indicated and not to use alternative strategies that increase the incidence of other, more common, complications such as laryngeal trauma due to tracheal intubation of inadequately relaxed patients [29].

Postoperative residual curarisation

Background

Ideally, to exclude any postoperative residual effect of a NMB, the drug should be completely metabolised to inactive substances or excreted by the end of anaesthesia. However, in reality, at the end of anaesthesia some of the injected NMB is commonly still present and active in the body, causing a partial neuromuscular block that can be difficult to diagnose clinically [30–32]. Paton and Waud [33] showed many years ago that as many as 70–80% of the nicotinic receptors at the postsynaptic membrane of the neuromuscular junction may be occupied by a non-depolarising NMB without any demonstrable adverse clinical effect. Further, the huge variability in the clinical response to NMBs, especially the aminosteroidal NMBs, makes it impossible to predict which patients will suffer postoperative residual curarisation (PORC). It is therefore important that the clinician knows the signs, symptoms, tests and management of PORC in order to diagnose and treat it.

Definition of postoperative residual curarisation

For many years a train-of-four (TOF) ratio of 0.7 was considered sufficient to exclude PORC [34]. Clinically, this level of neuromuscular block is associated with the ability to maintain a 5-s head lift [34] and hand grip, to protrude the tongue, as well as a return to normal upper eye-lid tone and jaw tone, and recovery to an adequate tidal volume, vital capacity and inspiratory force [31, 35, 36]. However, in recent years, several reports have documented that a TOF ratio of 0.7 does not guarantee sufficient neuromuscular recovery and today's general consensus is that to exclude clinically significant PORC, the TOF ratio should be ≥ 0.9 [37–39]. Table 1 shows some of the effects of partial block (TOF ratio = 0.7–1.0) in healthy awake volunteers. It is important to note that many of the signs and symptoms might be misinterpreted as residual effects of anaesthetic and opioids drugs in the postoperative setting, but are in fact residual block of the nicotinic receptors of skeletal muscles or in the carotid body

Table 1 Clinical effects of partial neuromuscular block in healthy un-anaesthetised volunteers.

Author	Signs and symptoms of postoperative residual curarisation
Eriksson et al., 1992 [40]	At a TOF ratio of 0.7 there was Markedly reduced ventilatory response to hypoxaemia Diplopia and ptosis Difficulty swallowing Difficulties in fixing a mouthpiece
Eriksson et al., 1993 [41]	At a TOF ratio of 0.7 there was Markedly decreased ventilatory response to hypoxaemia
Eriksson et al., 1997 [42]	At a TOF ratio < 0.9 there was Dyscoordinated swallowing with episodes of aspiration Reduction in upper oesophageal sphincter function Dyscoordination between pharyngeal constrictor and oesophageal sphincter Diplopia, dysarthria and difficulty in swallowing
Kopman et al., 1997 [43]	At a TOF ratio of 0.7 All volunteers felt very uncomfortable Speaking required great effort At a TOF ratio of 1.0 One patient experienced difficulty in swallowing
Sundman et al., 2000 [44]	At a TOF ratio < 0.9 there was Impaired pharyngeal function and airway protection Dyscoordinated swallowing At a TOF ratio ≥ 0.9 there was Still pharyngeal dysfunction in a few subjects Still dyscoordinated swallowing in a few subjects 15 min after a TOF ratio > 0.9 had been achieved, there was Still pharyngeal dysfunction in a few subjects
Eikermann et al., 2003 [50]	At a TOF ratio of 0.8 Respiratory function and pharyngeal function was impaired At a TOF ratio of 1.0 Respiratory function and pharyngeal function was impaired in a few subjects
Eikermann et al., 2004 [51]	At a TOF ratio of 0.91–0.95 Respiratory function had recovered in the vast majority of subjects At a TOF ratio of 1.0 Respiratory function was still impaired in a few subjects

[40–49]. Surprisingly, even at a TOF ratio > 0.9 or 1.0 measured at the adductor pollicis muscle, some subjects still have impaired pharyngeal or respiratory function [43, 44, 47, 48, 50–52]. This might be explained by a difference in sensitivity to NMBs in different muscle groups [53]. In addition, the residual effects of anaesthetics and opioids in the postoperative setting magnifies the effects of PORC [44, 47, 49] and increases the risk of respiratory complications [54], morbidity and mortality [55].

The incidence of postoperative residual curarisation

Almost 30 years ago the first paper documented that PORC (defined as TOF ratio < 0.7) was a significant problem in the recovery room after administration of long-acting NMBs [56]. These results have been confirmed several times, showing the incidence of PORC to be 25–85% if the neuromuscular block is not monitored [57–61]. The use of intermediate-duration NMBs decreases not only the incidence of PORC [54, 61–65] but also the incidence of postoperative respiratory complications [54]. Nevertheless, the use of intermediate-duration NMBs is also associated with PORC. Incidences varying between 15% and 88% have been reported, with the highest incidences following short surgical procedures [61, 66–71]. However, a longer duration of surgery does not exclude PORC after the use of intermediate-duration NMBs. Debaene et al. [70] found that 37% of patients suffered PORC after more than 2 h of anaesthesia when a single intubation dose ($2 \times ED_{95}$) of an intermediate-duration NMB was given. After 4–8 h some patients still had a TOF ratio < 0.9 [70, 72]. This emphasises the huge clinical variability in duration of action of all NMBs. Although the amino-steroidal NMBs have a greater variability than the benzylisoquinolines [73, 74], even the use of these latter drugs can lead to a high incidence of PORC [66, 68, 70, 74].

Table 2 Clinical signs and symptoms of postoperative residual block.

Unspecific and unreliable symptoms
Generalised fatigue
Diplopia
Unspecific and unreliable tests
Vital capacity below normal
The patient is unable to
Sustain eye opening
Protrude the tongue
Lift arm to the opposite shoulder
Create an inspiratory pressure ≥ −25 cmH_2O
Unspecific but more reliable tests
The patient is unable to
Sustain head lift for 5 s
Sustain leg lift for 5 s
Sustain hand grip for 5 s
Sustain tongue depressor test
Create an inspiratory pressure ≥ −50 cmH_2O

Clinical tests of residual block

The clinical tests commonly performed at the end of anaesthesia to ensure sufficient recovery of neuromuscular function are unspecific and unreliable, and most of them require an awake and cooperative patient (Table 2) [37, 43, 58, 59, 61, 70, 75–77]. Nevertheless, judging from the sparse use of nerve stimulators during routine anaesthesia around the world [78–81], the clinical tests are often the only monitoring used by anaesthetists to ensure sufficient recovery at the end of anaesthesia. It would therefore be expected that anaesthetists have a thorough knowledge of both the tests and their reliability, and that they use the most reliable tests in clinical practice. However, according to a recent Danish study, this seems not to be the case [80]. In this study it was documented that > 50% of the 251 anaesthetic nurses and anaesthetists studied were unable to distinguish between very unreliable and more reliable clinical tests, and < 50% routinely applied the more reliable clinical tests.

In spite of the uncertainties associated with the use of clinical tests, in reality these tests are often the only methods available to the anaesthetist for diagnosing PORC. It is therefore imperative not only that the anaesthetist has a thorough knowledge of the tests but also that the clinical tests are performed carefully and not, as is sometimes the case, carelessly!

Subjective monitoring

Subjective monitoring, i.e. visual or tactile evaluation of the response to nerve stimulation, may decrease the risk of PORC but does not exclude it [59, 82–85]. At TOF ratios of 0.3–0.4 it is usually not possible to feel or see fade in the TOF response [86]. Double-burst stimulation (DBS) increases sensitivity but fade in the DBS response cannot usually be felt or seen at a TOF ratio of ≥ 0.6 [87]. Relying on tactile or visual evaluation of fade after a 50 Hz or 100 Hz tetanic stimulation is also unreliable [88–90]. Feeling or observing fade in response to 100 Hz tetanic stimulation probably has the highest sensitivity in diagnosing PORC [90, 91]. However, some patients show fade even without exposure to a NMBA. Neither DBS nor tetanic stimulation should be performed in awake patients since both stimulation patterns are very painful.

Objective monitoring

As with subjective monitoring, objective monitoring, i.e. actual quantification of the TOF ratio, can help the

clinician when timing the administration of a reversal agent, but only with objective monitoring is it possible to exclude potentially clinically significant PORC (TOF ratio $\leq$ 0.9). Every paper published so far on objective monitoring has documented a significant decrease in PORC when objective monitoring was used [58, 67, 71, 75–77, 92, 93]. Good practice based on evidence therefore dictates that objective monitoring should be the acceptable standard of care whenever a NMB is used. Nevertheless, in many departments throughout the world, objective monitoring is not the standard of care. In the latest report by the American Society of Anesthesiologists Task Force on Postanesthetic Care it is stated that 'assessment of neuromuscular function should be performed…for patients receiving non-depolarizing NMBs or who have medical conditions associated with neuromuscular dysfunction' [94]. A recent meta-analysis of the monitoring of neuromuscular monitoring did not find an associated decrease in the risk of PORC [85]. However, neither this paper nor the American Society of Anesthesiologists Task Force on Postanesthetic Care report distinguishes between objective and subjective monitoring. In contrast, we recently documented in a systematic review that there is evidence for using acceleromyography in order to decrease the risk of PORC [95]. Objective monitors for clinical use, whether based on acceleromyography or kinemyography, are not foolproof, and they are more cumbersome to set up than other standard monitoring equipment in the operating room such as pulse oximetry, ECG and non-invasive blood pressure. These factors, the lack of recommendations from scientific societies and the price of a neuromuscular monitor (approximately €1000) might explain why objective neuromuscular monitoring is still not standard practice, although it is the gold standard for the exclusion of PORC.

Reversal of neuromuscular block

Reversal of neuromuscular block with cholinesterase inhibitors accelerates recovery. However, if reversal is performed too early, the block is often insufficiently reversed, increasing the risk of PORC [96–98]. In addition, standard reversal, e.g. neostigmine 50–70 $\mu g.kg^{-1}$, for all patients when there are between two and four measurable responses to TOF stimulation does not guarantee sufficient recovery. Several studies have documented high incidences of PORC (17–88%) with routine reversal of the neuromuscular block [67–69, 76, 93, 98]. In this context it is important to note that reversal with a cholinesterase inhibitor such as neostigmine during late recovery may enhance the neuromuscular block rather than antagonise it [99–102].

Suxamethonium

Suxamethonium consists of two acetylcholine molecules joined together by a methyl group. It is metabolised by plasma cholinesterase (pseudocholinesterase, acetylcholine acyl-hydrolase, EC 3.1.1.8). The structural similarity to acetylcholine makes it the NMB with the fastest onset (30–60 s). However, this similarity is also responsible for its many adverse effects caused by stimulation of receptors other than the acetylcholine receptors of the neuromuscular junction, such as the muscarinic receptors and receptors in the autonomic ganglia. Because of its many adverse effects clinicians commonly consider suxamethonium to be indicated only to gain control of the airway in emergency situations. Furthermore, the US Food and Drug Administration has issued a general warning against the use of suxamethonium in children (except for emergency control of the airway) and in adults at risk of hyperkalaemia. Injection of a small dose (10%) of a non-depolarising NMB (precurarisation or pretreatment) before giving suxamethonium may prevent some of the adverse effects but this technique should not be used in emergency situations because of the resulting unpredictable or prolonged action of suxamethonium. Table 3 shows the adverse effects associated with suxamethonium.

The duration of action of suxamethonium is determined by the rate of its hydrolysis by plasma cholinesterase [103]. The biosynthesis of plasma cholinesterase is controlled by more than 40 different genotypes, some of which give rise to an abnormal and most often decreased enzyme activity in plasma, leading to a prolonged response to suxamethonium (Table 4). In a Caucasian population 24% of subjects carry at least one cholinesterase variant, and the prevalence of clinically significant heterozygous and homozygous patients is about 1 : 40 and 1 : 2500 respectively [104]. The prevalence may be much lower in other populations. Although low plasma cholinesterase activity can also be related to many other factors (Table 5), non-genetically determined low plasma cholinesterase activity rarely gives rise to a significantly prolonged duration of action of suxamethonium. In most cases full muscle power is restored within 20–30 min.

The management of a patient with a prolonged response to suxamethonium depends on the plasma cholinesterase activity and genotype [105]. However, in the clinical situation, the patient's plasma cholinesterase activity and genotype are usually unknown. Therefore, attempts at reverting the block should be avoided and the patient should be kept anaesthetised and their lungs ventilated until fully recovered from the block. Specifically, injection of a cholinesterase inhibitor such as neostigmine in a patient with a genetically-determined

Table 3 Some adverse effects of suxamethonium.

Adverse effect	Risk factors	Management
Cardiovascular		
Increase in blood pressure and/or heart rate	High dose of suxamethonium	
Decrease in blood pressure and/or heart rate	Low dose of suxamethonium	
Bradycardia	Usage in children	Administration of atropine or glycopyrrolate
Cardiac arrest	Repeated doses of suxamethonium	
Arrhythmias	Pre-existing heart disease	
Acute rhabdomyolysis (risk of hyperkalaemia and cardiac arrest)	Skeletal muscle myopathies such as Duchenne's muscular dystrophy	
Hyperkalaemia	Extensive burn injury, multiple trauma, extensive denervation of skeletal muscles and upper motor neuron injury Risk highest 7–19 days after injury	Suxamethonium contraindicated
Myalgia	High dose of suxamethonium Usage in young adults and females Most pronounced in muscles in neck, back and shoulders	Pre-treatment with a non-depolarising NMB (10% ED_{95}) Peri-operative treatment with non-steroidal anti-inflammatory drugs
Fasciculations	Not related to myalgia	Pre-treatment with a non-depolarising NMB (10% ED_{95})
Trismus/masseter spasm*	Usage in children	
Increase in intragastric pressure	Might be related to fasciculations Hypothetical risk of pulmonary aspiration is not proven	
Increase in intra-ocular pressure	Pre-existing increased intraocular pressure Open eye injury	Suxamethonium relatively contraindicated
Malignant hyperthermia	Only NMB that may trigger hyperthermia Genetic predisposition Combination with potent inhalational anaesthetics	

*May be a sign of malignant hyperthermia.

Table 4 Recovery times after the administration of suxamethonium 1 $mg.kg^{-1}$ to patients who are phenotypically normal or abnormal with respect to plasma cholinesterase.

Phenotype	Time to first response to train-of-four stimulation; min	Time to sufficient recovery (train-of-four ratio ≥ 0.9); min
Normal	5–10	10–15
Heterozygous for the usual and at least one of the abnormal genes	10–15	15–25
Homozygous for two abnormal genes	40–60	120–180

Table 5 Causes of non-genetically determined decreased plasma cholinesterase activity.

Cause	Examples
Physiological variation	Pregnancy, newborn
Disease	Burns, liver or kidney disease, cancer, plasmapheresis, chronic disease
Iatrogenic	Neostigmine, bambuterol, hormonal contraception
Poisoning	Organophosphates

abnormal plasma cholinesterase activity may intensify rather than antagonise the block [105].

Non-depolarising neuromuscular blocking drugs

Traditionally, modern non-depolarising NMBs are divided into two classes based on their chemical structure: the benzylisoquinolines and the aminosteroidal compounds. Previously, this classification was important as the adverse effects tended to be similar for NMBs of the same class: aminosteroidal compounds were vagolytic and the benzylisoquinolines often released histamine. However, newer NMBs do not necessarily display the same adverse effects despite structural similarities. Accordingly, the adverse effects of the different non-depolarising NMBs are discussed separately.

Mivacurium

This short-acting benzylisoquinoline derivate is metabolised by plasma cholinesterase. As is the case with suxamethonium, the duration of action is therefore determined by the rate of its hydrolysis by this enzyme. However, the rate of hydrolysis is significantly slower than that of suxamethonium. Therefore, decreased plasma cholinesterase activity, whether caused by genetic or non-

Table 6 Recovery times after the administration of mivacurium 0.2 $mg.kg^{-1}$ to patients who are phenotypically normal or abnormal with respect to plasma cholinesterase.

Phenotype	Time to first response to train-of-four stimulation; min	Time to sufficient recovery (train-of-four ratio ≥ 0.9); min
Normal	10–15	25–45
Heterozygous for the usual and at least one of the abnormal genes	15–35	30–60
Homozygous for two abnormal genes	120–480	180–640

genetic factors, results in more prolonged durations than seen after suxamethonium (Table 6).

The management of a patient with a prolonged response to mivacurium should be conservative and expectant, as for suxamethonium. The patient should be kept anaesthetised and their lungs ventilated until the TOF ratio is ≥ 0.9 [106–108]. Unless human cholinesterase (which is rarely available) is injected before neostigmine, the effect of the neostigmine is unpredictable and may intensify rather than antagonise the block [108].

Mivacurium releases histamine in relation to high doses, i.e. ≥ 0.20 $mg.kg^{-1}$ (≥ 3 × ED_{95}), and rapid injection, i.e. < 30 s. The increase in histamine level may result in skin flushing and, in rare cases, produce transient hypotension, tachycardia, urticaria and bronchospasm 1–5 min after injection. The decrease in blood pressure and the compensatory increase in heart rate can be minimised by injecting mivacurium slowly over 30–60 s. Mivacurium was withdrawn from use in several countries (including the US) in 2007 for market reasons but is still available in most European countries [109].

Atracurium

This intermediate-duration benzylisoquinoline derivative undergoes Hoffmann elimination and hydrolysis by non-specific esterases. Laudanosine is one of the metabolites, and after long-term use in the intensive care unit or in patients with hepatic failure, high laudanosine levels may – in theory at least – result in central nervous system excitation. Atracurium in high doses, i.e. ≥ 0.6 $mg.kg^{-1}$ (≥ 3 × ED_{95}) may increase plasma histamine levels transiently, but only rarely causes a significant decrease in blood pressure or other histamine-related symptoms. The variability in duration of action is somewhat less than that of the aminosteroidal NMBs.

Cisatracurium

This intermediate-duration benzylisoquinoline derivative is, like atracurium, mainly metabolised via the organ-independent Hoffmann elimination process. However, the resulting plasma concentration of laudanosine is significantly lower than that following atracurium and appears to be of no clinical significance even after long-term use in intensive care units. In contrast to the other benzylisoquinolines mivacurium and atracurium, cisatracurium does not cause any dose-dependent increase in plasma histamine level, and rapid intravenous administration does not cause cardiovascular changes. As with atracurium, the variability in duration of action is somewhat less than that of the aminosteroidal NMBs.

Vecuronium

Vecuronium is an intermediate-duration aminosteroid with no vagolytic or histamine-releasing effects. It is mainly excreted in the bile but also undergoes some renal excretion. One metabolite, 3-desacetyl vecuronium, is thought to have 50% of the potency of vecuronium. However, the metabolite is without clinical significance unless vecuronium is used in long-term administration in intensive care units. As with the other aminosteroids rocuronium and pancuronium, the variability in response to vecuronium is quite pronounced, not least after repeated doses.

Rocuronium

Like vecuronium, this intermediate-duration aminosteroid has no vagolytic or histamine-releasing effects, but unlike vecuronium it has a rapid onset, making it an alternative to suxamethonium in rapid sequence induction. Rocuronium is mainly cleared unchanged in the bile but is also excreted by the kidneys. It has no active metabolites. As with the other aminosteroids vecuronium and pancuronium, the variability in response to rocuronium is quite pronounced, not least following repeated doses.

Pancuronium

This long-duration aminosteroid is mainly excreted by the kidneys, but 10–40% of the administered dose undergoes hepatic metabolism. One of the metabolites, 3-desacetyl pancuronium, has 50% of the potency of pancuronium. Pancuronium binds to muscarinic receptors in the heart (sino-atrial node) and inhibits the release and reuptake of noradrenaline, causing vagolysis and an increase in heart rate and blood pressure. Pancuronium may cause severe tachyarrhythmias that appear to be related to pre-existing heart disease such as atrial fibrillation or an interaction with other drugs, e.g. tricyclic antidepressants, rather than to the dose of pancuronium. Direct stimulation of the heart may increase myocardial oxygen consumption and cause cardiac ischaemia in patients with coronary artery disease. Pancuronium has no effects on the autonomic ganglia and does not release

histamine. Due to its long duration of action, its propensity to cause PORC is marked if the neuromuscular block is not monitored objectively [58]. Furthermore, it has been documented that PORC following the use of pancuronium may lead to respiratory complications [54].

Conclusions

The French humorist and actor Maurice Chevalier was once asked about his advancing age. His often-quoted reply was 'Considering the alternative…it's not too bad at all'. It is exactly the same with the NMBs. Yes, there are certainly undesirable effects of using NMBs. However, considering the alternative, they are not that bad! We agree with the old adage 'do not throw the baby out with the bathwater'. Do not forget the undesirable effects of *not* using NMBs. As noted in the section on hypersensitivity reactions: use the NMBs when indicated – and do not use alternative strategies that may increase the rate of other complications such as laryngeal trauma due to inadequately relaxed patients [29].

Conflicts of interest

All authors have served on expert advisory boards and received research grants, speakers' fees and honoraria from Schering-Plough. However, they have no shares or options in any pharmaceutical company and this study was not supported by grants from any company.

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