Neuromuscular Blocking Agents: Review on Agents (NMBA and Antagonists) and Monitoring

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Beatrice Penzo, Laura Petrò, and Andrea DeGasperi

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4.1 Introduction

The use of (NMBAs) in clinical anesthesia has its origins in compounds with paralytic effects (poisons) put on the arrows by the pre-Colombian Indians of South American: the principles date back centuries. In 2015, Barash et al. [1] ranked 13th, among the seminal articles in the history of clinical anesthesia, the paper written in 1942 by Griffith and Johnson [2] on the use of curares in general anesthesia ("*curares*" today are better defined as neuromuscular blocking agents [NMBAs] or neuromuscular blocking drugs [NMBDs]). Recently, Brull and Kopman [3] classified as relevant in this specific setting the study proposed in 1954 by Beecher and Todd dealing with deaths in anesthesia: compared to 1:2000 mortality without the use of curares, a ratio of 1:370 was reported when curares were employed [4].

To Egidio Maestrone, MD

B. Penzo · L. Petrò · A. DeGasperi (✉)
2° Servizio Anestesia e Rianimazione—ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: beatrice.penzo@ospedaleniguarda.it; laura.petro@ospedaleniguarda.it; andrea.degasperi@mpcnet.it, andrea.degasperi@ospedaleniguarda.it

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The introduction in clinical anesthesia of an extremely efficient solution to a relevant technical surgical problem (muscle relaxation to ease the surgical approach) started the modern era of surgery, making possible extraordinary development in major surgical procedures. However, neuromuscular monitoring for the optimal use of NMBAs and to avoid new dangerous threats became, and is at present, mandatory [5]. Deep muscular blocking and/or muscle paralysis should not be confounded with good quality of depth of anesthesia, by definition the combination of loss of consciousness and analgesia. Indeed, a UK study (NAP5) recently pointed out the relevant role (97%) played by muscle relaxants in awareness (consciousness) during general anesthesia [6]. Hence, the role of both neuromuscular monitoring and anesthesia depth is pivotal to prevent relevant negative physiological responses to the surgical trauma in a patient paralyzed (optimal operating conditions), but since still somehow conscious and "responsive" (not under anesthesia), able to feel pain. As stated by Naguib et al. [5], the inappropriate use of muscle relaxants to cover deficiencies in anesthesia management represents a relevant misuse of a valuable adjunct to anesthesia. Furthermore, NMBAs are not devoid of side effects on cardiovascular and respiratory apparatus (vide infra), and are associated with allergic reactions, muscle relaxants being responsible for the majority of allergic and anaphylactic reactions in anesthesia and of pharmacological interactions [5, 7, 8].

The use of NMBAs is on the rise. A recent audit on the anesthesiological activity in the UK showed that close to half of general anesthesia cases included in the pharmacological armamentarium muscle relaxants [9]. In a review on the use of NMBAs in the elderly population [10] (a growing "special" population among surgical patients, due to an increasing life expectancy together with extended surgical indications), Lee et al. identified the following as pivotal issues associated with the use of NMBAs:

1. The role of NMBAs in ventilation and intubation: the issue of myoresolution in difficult airways management is crucial; for this specific item, refer to Difficult Airways Society Guidelines, DAS 2018, (https://das.uk.com/guidelines) [11, 12]
2. The importance of a rapid, highly selective antagonist ("reversal") available in case of "cannot-intubate-cannot-ventilate".
3. The degree of block and the surgical technique: if the surgical access is made easier by myoresolution, the degree of the muscular block should be proportionate to the type of surgical technique (laparotomic or laparoscopic).
4. The place of residual curarization (post-operative residual curarization, the *PORC* phenomenon) as a relevant cause of postoperative complications, mainly respiratory; this issue, very well known in the past [13], is still relevant nowadays and could be found in "special" patients populations": elderly or obese patients, those affected by neuromuscular illness, multiple organ dysfunction, or when particular pharmacological techniques are used (deep neuromuscular blocking) [7, 9, 10]

In these specific settings, a rapid and reliable reversal, as is available today with sugammadex for aminosteroidal NMBAs, enables fast and safe recovery of

muscular function; however, failures, even if rare, are possible, as stated in a very recent Cochrane review (2017) [14].

A very recent seminal review article [15] underlines the relevance of monitoring the neuromuscular function (NMFM, neuromuscular function monitoring) when using NMBAs, both in anesthesia and ICU; the target should be an *objective* and *quantitative* NMFM, instead of a clinical, qualitative, and subjective assessment. The opportunity provided by safe and reliable reversal agents (such as sugammadex at present and with L-Cysteine in the near future) should not replace neuromuscular monitoring. Indeed, NMFM is able to demonstrate the need for reversal even in cases where its use was deemed unnecessary [5, 15–17]. With minimal technical risks associated with the modern dedicated devices, NMFM enables much safer anesthesia management and an easier and reliable recovery from muscle paralysis, minimizing the rate of rare but potentially fatal devastating complications [5, 7, 15–17].

4.2 Neuromuscular Blocking Agents (NMBAs): The Classification [5, 7, 8, 10, 16, 18]

NMBAs are classified according to their ***mechanism of action*** in *depolarizing* and *nondepolarizing* compounds [5, 7, 8, 10, 18]. This classification is mainly driven by the interaction between **acetylcholine** (**ACh**) and acetylcholine **nicotinic receptors (AChRs)** on a neuromuscular junction (NMJ) [19]. The only available *depolarizing* agent is *succinylcholine* (SCh), whose use dates back to 1952. Modern *nondepolarizing* agents are classified according to their ***chemical structure*** (steroidal vs. benzylisoquinoline derivatives) as well as their ***duration of action*** (short, intermediate, long-acting compounds). They include ***aminosteroids*** (mainly *vecuronium* and *rocuronium;* pancuronium, a time-honored blocking agent, being pulled from the market in the majority of the developed countries) and ***benzylisoquinoline derivatives***; among the latter are short-acting (*mivacurium,* very seldom used, and not discussed in this chapter) and intermediate-acting agents (*atracurium* and *cisatracurium*).

The type of neuromuscular blockade (*depolarizing* or *nondepolarizing*) defines the specific reaction, after peripheral stimulation, used to evaluate the degree and the quality of block [7, 15–19].

4.2.1 Neuromuscular Junction and Basic Physiology of Neurotransmission [5, 15, 18, 19] (Fig. 4.1)

Three main components of the nicotinic neuromuscular junction (synapse) are the distal part of motor nerve (axon), the post synaptic motor end plate (in particular the muscle fiber membrane), and the Schwann cell. Between the motor nerve terminus and the muscular end plate, there is a gap. This structure allows a unidirectional chemical communication between a peripheral nerve and the muscle fiber. The

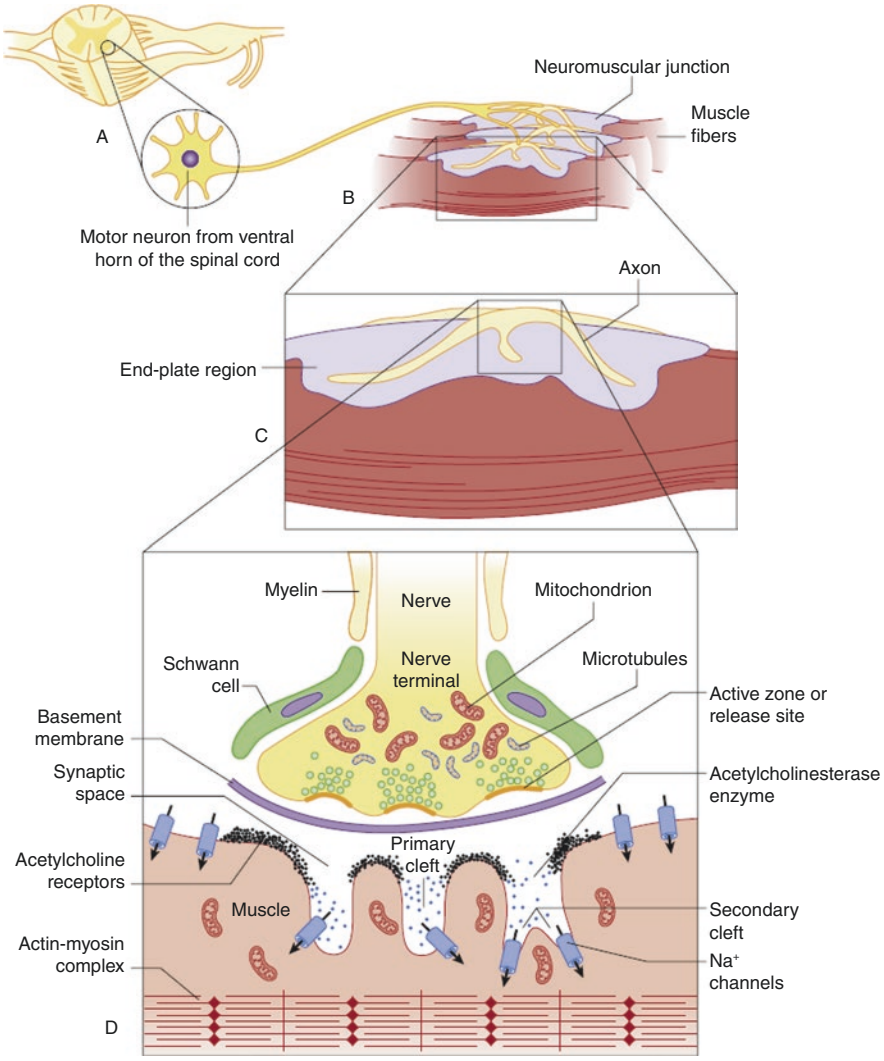

Fig. 4.1 The adult neuromuscular Junction (synapse): motor neuron (i.e., nerve terminal), muscle fiber, and Schwann cells covering the nerve terminal. From Martyn JAJ. Neuromuscular physiology and pharmacology. Chapt 18. In: Miller RD, Eriksson LI, Fleisher L, Wiener Kornish JP, Cohen M, Young WL, editors. Miller's anesthesia. 8th ed. Elsevier; 2015. p. 423–43. (**a**) Motor nerve origin. (**b**) Muscle fiber innervation. (**c**) End-plate region. (**d**) Neuromuscular junction. (1) Nerve terminal covered by Schwann cells. (2) Active zones with vesicles clustered close to membrane thickenings. (3) Synaptic space between the nerve and the muscle (cleft). (4) Corrugated muscle surface (due to the presence of primary and secondary clefts). (i) Cleft shoulders: Ach receptors in dense areas. (ii) Cleft bottom: Sodium (Na+) channels (throughout the muscle membrane). (5) Acetylcholinesterase in the synaptic clefts

nerve, originating from the brainstem or from the ventral horn of the spinal cord and approaching the muscle, divides into branches directed to the membrane of muscles fibers for their innervation. The motor nerve, having lost myelin sheath but covered by the Schwann cells, terminates with many presynaptic buttons (*presynaptic nerve terminal*) in front of the surface of the muscle fiber (*postsynaptic endplate*). The nerve terminal and the muscle membrane are separated by a space, (gap) the synaptic space or *cleft* (20–50 nm). Nerve and muscle ends are kept tightly aligned by protein filaments (basal lamina). The nerve terminal has membrane thickenings close to which clustered vesicles containing ACh are harbored (*active or release* zone). Voltage-gated Ca channels embedded in the nerve membrane and organelles (mitochondria and microtubules) are also present. On the opposite site of the space, the muscle surface is highly corrugated due to the presence of deep invaginations, creating primary and secondary clefts, thus enlarging the surface area. ACh receptors are highly expressed on the top of the invaginations (the "shoulder" of the cleft), while sodium channels are highly represented at the bottom of the clefts and across the muscle membrane [14]. The nicotinic cholinergic receptors (AChRs), synthesized in muscle cells and anchored to the endplate membrane, are formed of five subunits ("the staves of a barrel") and define a cylindrical receptor with a central hole (*pore*) for ion channeling. In the mature receptor, two of the five subunits are α_1, (β_1, δ, and ε are the three others). Each α_1 subunit has the Ach-binding site that is able to attract both agonists and antagonists, thus being a site of possible competition. The pore of the channel is usually closed by subunit apposition. Stimulation of the nerve (action potential from the nerve terminus) causes migration of vesicles toward the nerve surface, rupture of vesicles (exocytosis), and ACh release into the synaptic clef (quantal theory). The occupation of the two α subunit sites by an agonist (Ach in this case) results in the opening of the central channel after a structural rearrangement; ions (mainly cations) flow along a concentration gradient (Na^+ and Ca^{++} from outside to inside; K^+ from inside to outside) and the current transported by the ions depolarizes the adjacent membrane (*muscle stimulation*), creating the endplate potential and the generation of the muscle contraction. Closure of the channel is usually initiated when one (or both agonists) is detached from the receptor. ACh detaches immediately from the receptor to be destroyed by AChEsterase (ACE), an enzyme secreted from the muscle and redundant in the synaptic cleft; muscle contraction (the result of the depolarization) ends when ACh dissociates from its receptor, so that myocyte membrane can repolarize. This is the mechanism of action of depolarizing NMBAs (succinylcholine, SCh), carbacol (ACh synthetic analog not affected by ACE action), and nicotine, mimicking ACh effect at the motor endplate (depolarization) and defined as *AChRagonists* [18, 19].

Interestingly enough, nondepolarizing muscle relaxants (vide infra) act on AChRs with a completely different mechanism, preventing binding of ACh to receptors and, by consequence, the depolarization induced by agonists; then, nondepolarizing muscle relaxants are defined *AChRs antagonists* [8, 16, 18, 19]. ACE action is *reversibly* blocked by inhibitors (edrofonium, pyridostigmine, neostigmine), whose main mechanism is ACh hydrolysis block. The accumulation of ACh creates a strong competition at the AChRs with nondepolarizing muscle relaxants, which are

displaced from the receptors by mass action: this is the mechanism at the base of antagonization of nondepolarizing muscle relaxants [5, 7, 17, 18]. On the contrary, ACEs are *irreversibly* blocked by pesticides (organophosphates) or sarin gas. Just as important, with a possible relevant impact on clinical anesthesia, channel opening and closing is affected by physical (temperature) or chemical (pH) changes and by pharmacological interactions (among others, the sum of the individual or synergic effects).

4.3 Depolarizing Neuromuscular Blocking Agents: Succinylcholine (SCh) [7, 8, 10, 18, 19] (Fig. 4.2)

From the outset, SCh (succinylcholine or suxamethonium), introduced by Thesleff and Foldes in 1952, greatly impacted clinical anesthesia practice due to its favorable pK/PD characteristics. It is a small, "flexible" molecule, as defined by Bovet and composed of two ACh molecules linked through the acetate methyl groups. The presence of two quaternary ammonium cations mimics the quaternary nitrogen of ACh and its affinity for nicotinic receptors on NMJ, a feature shared by all the NMBAs. It acts as a partial antagonist by binding to the two α subunits of the AChR, leading to a much longer and persistent post synaptic membrane depolarization compared to the rapidly degraded Ach. As an NMBA, SCh remains longer in inter-synaptic space, keeping ion channels open and thus maintaining a continuous end-plate depolarization; Na^+ channels are inactivated, preventing the development of an action potential in the muscle fiber. SCh has a rapid onset and ultrashort duration of action. Cholinergic receptor desensitization reduces agonist effect. Neuromuscular plaque depolarization starts with fasciculations (fast, spontaneous, and intermittent contractions of muscle fibers) within 30 s from administration; flaccid paralysis will rapidly ensue, usually within 60 s [11–14]. Fasciculations are almost always present with mature receptors and may be prevented using a small dose (1/10 of the usual

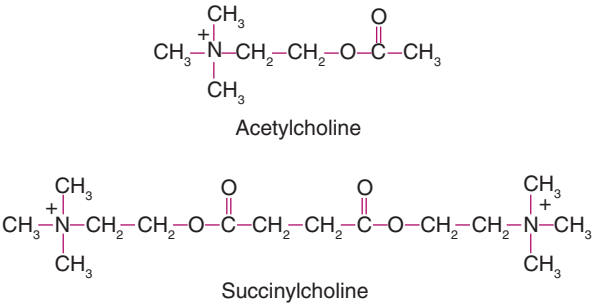

Fig. 4.2 Chemical structures of Acetylcholine and Succinylcholine. (From Naguib M, Lien CA, Meistelman C. Pharmacology of neuromuscular blocking drugs. Chapt 35. In: Miller RD, Eriksson LI, Fleisher L, Wiener Kornish JP, Cohen M, Young WL, editors. Miller's anesthesia. 8th ed. Elsevier; 2015. p. 965–99)

dosage) of a nondepolarizing NMBA before SCh administration. This sort of "precurarization" may not bring substantial advantages, while potentially causing adverse effects; among them are partial resistance to SCh, need for a higher dose, action time prolongation, postoperative myalgia (in part attributed to fasciculations), partial muscular block paralysis in a still-conscious patient, inhalation risk. Nowadays, SCh, even if still used and considered a reference standard for rapid sequence intubation, is not advised or recommended [7, 8, 18].

SCh in dose of 1 to 1.5 mg/kg ensures onset of the neuromuscular block within 60 s (flaccid paralysis), and recovery of muscle tone (90%) in 7–13 min in patients with normal pseudocholinesterase (also known as plasma cholinesterase, vide infra) [7, 8, 16, 18, 19]. The half-life of SCh is less than 1 min, the volume of distribution (V_d) is high (>30 mL/kg). In terms of pharmacodynamics (PD), the degree of blockade varies according to different muscles; it is short and intense in laryngeal muscles; diaphragm shows functional recovery within 5 min [13]. In fact, time to achieve optimal orotracheal intubation conditions with SCh is very short (< 60 s with doses of 1–1.5 mg/kg). Neuromuscular block induced by SCh is defined Type I block (different from type II, peculiar of nondepolarizing NMBAs, and present in case of high-dose SCh [7, 8, 18, 19]). Interruption of SCh action is due to its elimination from plasma by rapid and intense hydrolyzation by pseudocholinesterase (butyrylcholinesterase, BChE); the enzyme activity is reduced in case of hepatic failure, advanced age, use of MAO inhibitors, anticholinesterase agents (ACEIs), or due to congenital deficiency in genetic disorders. Reduction in pseudocholinesterase below 20% might be associated with a prolonged neuromuscular blockade. Prolonged paralysis using SCh (up to 4–8 h, often associated with postoperative awareness) can occur in case of atypical genetic variants of BChE, which respond differently to dibucaine (amino amide local anesthetic, DBC); DBC inhibits 80% of the normal BChE, but only 20% in case of abnormal BChE [7, 8]."DBC number" defines the percentage of inhibition of BChE by DBC, but not the concentration of the enzyme, measured by BChE activity in plasma. The normal value of DBC number is 70–80, associated with normal response to SCh or Mivacurium. In case of heterozygous atypical BChE, the DBC number is 50–60, with lengthening of SCh response by 50–100%. In case of homozygous atypical BChE (reported in 1/3200 cases), the DBC number is 20–30 and the response very prolonged (4–8 h) [8]. The use of SCh, very common until the start of the third millennium, is now declining; availability of rapidly acting nondepolarizing NMBA (rocuronium) and its specific antagonist (sugammadex), together with the relevant side effects, makes the use of SCh less common.

4.3.1 Side Effects [7, 8, 18, 19]

Despite its rapid onset of action, SCh has many relevant side effects, which prevent its widespread use nowadays.

Cardiovascular effects—SCh stimulates sinus node muscarinic receptors and sympathetic and parasympathetic autonomic ganglia cholinergic receptors.

Dysrhythmias, including bradycardias (up to prolonged asystole), junctional rhythm, idioventricular rhythm, ventricular extrasystoles may occur. Sinus bradycardia often occurs in pediatric patients, for whom atropine administration is recommended. Interestingly enough, the higher incidence of bradycardia after the second SCh dose could suggest a possible sensitization induced by SCh hydrolysis products on muscarinic receptors. Ventricular escape beats may be reported in case of severe bradycardia or in the presence of increased K^+ concentration, possible in case of skeletal muscle release secondary to SCh depolarizing action. Whether cardiac dysrhythmias are caused by SCh per se or because other autonomic stimulation is still under discussion.

Malignant Hyperthermia—SCh is one of the well-known triggers for malignant hyperthermia: it is contraindicated in case of positive medical history, familiarity, or suspicion of previous episodes of malignant hyperthermia.

Hyperkalemia—Standard SCh dose in healthy individuals increases plasma K+ levels by 0,2–0.5 mmol/L (secondary to ion channels activation and subsequent potassium outflow from muscle cell). This change might be prevented by a subclinical dose of NMBA (vide supra).

SCh use can be harmful in specific patient groups. A general consensus exists in the literature on SCh contraindication, due to possible exaggerated response, in Multiple Sclerosis, Lateral Amyotrophic Sclerosis (LAS), muscular dystrophies, in critically ill patients suffering for Critically Ill polyneuropathy (CIP), Guillain Barrè syndrome, stroke sequelae, burns, physical trauma, brain injury in polytrauma patients. In these patients, an increased number of extrajunctional cholinergic receptors, well documented since long, are considered responsible for this adverse effect. In case of trauma, adverse responses can be recorded within 1 week from the traumatic event. Muscle pain after SCh administration is widely reported; whether or not it can be prevented by pretreatment with NDMAs is still under scrutiny. Renal failure is not a contraindication unless resulting in hyperkalemia.

SCh should be avoided in cases of endocular pressure increase, as it causes 5–10 mmHg pressure increase, with peak at 2–4 min of normalization after 6 min [7, 8, 16–18]. This effect could be particularly feared in case of trauma and/or with anterior chamber injury (in case of open anterior chamber the SCh use is contraindicated). Nonetheless, the use of SCh has been successfully reported in case of penetrating eye injuries (pretreatment with nondepolarizing NMBAs together with "controlled" rapid sequence intubation could be a possible strategy) [18]. Nowadays, rocuronium (vide infra) could be a realistic and perhaps better alternative in these settings.

SCh is associated with increased intragastric pressure, a highly probable consequence of fasciculation. Regurgitation from the stomach has to be taken into serious consideration in this setting. Rise in Intracranial pressure (ICP) is also possible. Pretreatment with NDBAs (so-called precurarization) is used by some or suggested in daily clinical practice as able, according to some, to reduce fasciculation and ICP rise; however, it is not always effective and is possibly associated with side effects.

Challenging could be the possible interaction of SCh with AChE inhibitors (ACEIs). The classic scenario is the need for SCh for emergent reintubation in case

of laryngospasm after extubation with the prior use of neostigmine to antagonize residual NM block; the effect of SCh is amplified and prolonged [14].

4.4 Nondepolarizing Neuromuscular Blocking Agents (NDNMBAs)

Nondepolarizing muscle relaxants act as *competitive antagonists* targeting the postsynaptic α subunits of the postsynaptic nicotinic cholinergic receptor (nAChR); competing with ACh, NDNMBAs prevent ACh from binding to the receptor sites and the consequent action potential, resulting in flaccid paralysis. NDNMBAs can be classified according to (1) chemical class (aminosteroid vs. benzylisoquinoline compounds) or (2) onset and duration of action (short-acting 10–20 min, intermediate acting 20–50 min, long-acting >50 min) [11–14]. The presence of an acetyl ester (similar to ACh) facilitates their interaction on the postsynaptic muscle membrane. NDNMBAs bind to the receptor via the positive charges at the quaternary ammonium sites. The structural reason for the attraction of these molecules to nAChRs resides in the quaternary nitrogen ammonium that mimics ACh quaternary nitrogen atom. A single-site blockade on an α subunit by a blocking agent is enough to prevent channel pore opening despite ACh binding to the second subunit, as underlined by Haberer [18]. The number of blocked receptors determines the degree of muscle paralysis. The type of block (first or second type) affects the response to the type of peripheral neurostimulation used for monitoring (see Monitoring paragraph).

As pointed out by Haberer [18] and Martyn [19], in modern anesthesia practice the definition ofNDNMBA potency becomes relevant. Usually, it is expressed as a dose-response relationship. The dose needed to produce a twitch height depression of 50%, 90%, or 95% and expressed as ED_{50} ED_{90} and ED_{95}, respectively, describes NDNMBA potency. It refers to the "pro kg" dosage able to induce the effect. Potency is inversely proportional to the speed of onset of neuromuscular blockade, the faster the onset, the less potent the drug; more potent compounds usually have a slower onset, while less potent drugs have a more rapid onset of action (see intubation conditions with cisatracurium and vecuronium compared to rocuronium) [7, 8]. Increasing the dose of some NDNMBAs up to a certain point (as is for rocuronium and perhaps for the new compound gantacurium) can speed up the onset of neuromuscular blockade; beyond this point, the onset time will not be shortened, with the possible increase of adverse effects, mainly consequences of increased (or prolonged) neuromuscular block. Then, high ED_{95} is the expression of low potency and predicts rapid onset and wean-off effects; the contrary is for more potent compounds, usually characterized by longer onset time and longer duration of effect [7, 8, 18, 19]. From the clinical point of view, among NDNMBAs, the more potent compound at the moment available, cisatracurium, has the slowest onset, while rocuronium, the least potent agent, possesses the faster onset. A plausible (but still not completely convincing) explanation of this phenomenon was proposed recently [8].

Table 4.1 Definitions of depth of neuromuscular block based on measured criteria

Monitoring	Post-Tetanic count (PTC)	Train-of-Four count (TOFc)	Train-of-Four ratio (TOFr)
Type of block			
Complete block	0	0	0
Deep block	>1	0	0
Moderate block	NA	1–3	0
Light (shallow) block	NA	4	0.1–0.4
Minimal block (immediatelybeforefunctional recovery)	NA	4	>0.4 < 0.9
Full recovery (normal functionalrecovery or acceptable recovery)	NA	4	>0.9–1

Modified from Brull and Kopman. Current status of neuromuscular reversal and monitoring. challenges and opportunities. Anesthesiology. 2017;126:173–90 and from Naguib M et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg. 2018;127:71–80

Neuromuscular block is not the same in different muscles or muscle groups; an example is the resistance to NDNMBAs of the laryngeal adductor muscle when compared to adductor pollicis. In spite of this, the onset of neuromuscular block is faster, the duration is shorter, functional recovery quicker in muscles crucial during tracheal intubation (laryngeal adductors, diaphragm, masseter) when compared to adductor pollicis (used for neuromuscular monitoring).

For the use in anesthesia and critical care settings (mainly endotracheal intubation for surgical anesthesia and in selected ICU patients), NDNMDA dose for endotracheal intubation can be defined as × 2–3 the ED_{95} (see Table 4.1). Interestingly, the degree of block of corrugator supercilii muscle, sometimes used in NM monitoring, is similar to that shown by laryngeal muscles, diaphragm, and abdominal wall, is more intense, with a shorter onset (1–2 min) when compared to that showed by adductor pollicis (TOF disappearance in corrugator supercilii muscle associated to optimal intubation conditions in more than 90% patients, although it is much less used than that of adductor pollicis) [5, 18]. The upper airway muscles, on the contrary, are more sensible than the adductor pollicis to the effects of NDNMBAs; recovery of adductor pollicis strength does not mean optimal recovery of upper airway muscles strength. A TOF rate below 0.9 at the adductor pollicis is associated from a practical clinical point of view with a decreased coordination of the muscles involved in airway protection and swallowing, making high the risk for aspiration early after extubation [5, 17].

NDNMBAs of both chemical classes are poorly fat soluble and highly water soluble; for steroidal compounds, elimination occurs via glomerular filtration and tubular secretion at different rates (*pancuronium, vecuronium*) or after more or less intense hepatic metabolism *(vecuronium, rocuronium*) [5, 10, 18, 19]. Benzylisoquinoline derivatives (*atracurium and cisatracurium*) are metabolized through two pathways (vide infra): nonspecific ester hydrolysis (negligible for cisatracurium) and Hofmann elimination (spontaneous degradation to laudanosine and monoquaternary acrylate, both compounds devoid of neuromuscular

activity and without clinically relevant cardiovascular effects). For laudanosine, central nervous system irritative properties were described in the animal model; the clinical significance in humans is, however, negligible. For atracurium, much less used today after the marketing of cisatracurium, routes different from ester hydrolysis and Hofmann and not completely understood are to be considered [7, 8, 18] (Fig. 4.3).

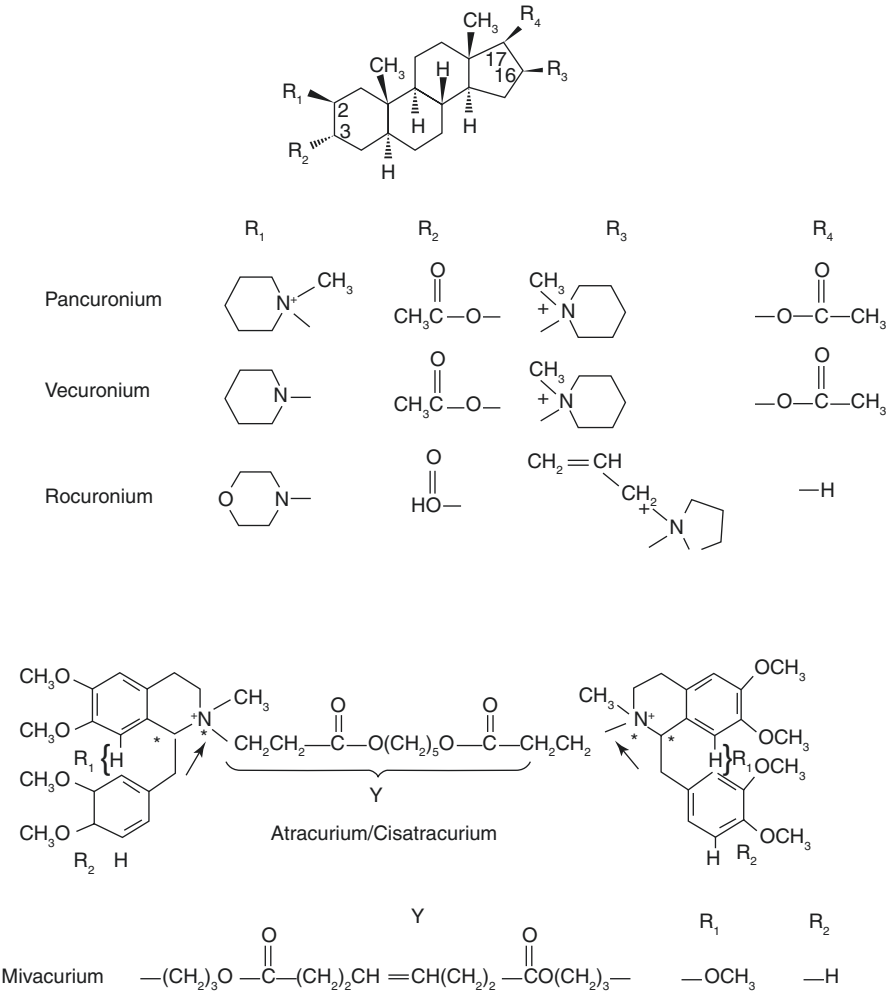

Fig. 4.3 Chemical structures of nondepolarizing neuromuscular blocking agents: Aminosteroidal agents (Pancuronium, Vecuronium, and Rocuronium) andBenzylisoquinoline derivatives (Mivacurium, Atracurium, and Cisatracurium). (From Naguib M, Lien CA, Meistelman C. Pharmacology of neuromuscular blocking drugs. Chap. 34. In: Miller RD, Eriksson LI, Fleisher L, Wiener Kornish JP, Cohen M, Young WL, editors. Miller's anesthesia. 8th ed. Elsevier; 2015. p. 958–94)

4.4.1 Aminosteroidal NDNMBAs

Among **steroidal NDNMBAs**, *rocuronium and vecuronium* are the most used compounds nowadays, and their pharmacokinetic and pharmacodynamic (pK/PD) properties will be described in the following content. *Pancuronium* is no longer available; *pipecuronium*, an extremely long-acting ND agent, has never been marketed in Italy.

Vecuronium (VEC) is a pancuronium demethylated derivative introduced in clinical practice in the 1980s. ED_{95} is 0.05 mg/kg (quite high potency). It is an intermediate-acting NDNMBA. Compared to pancuronium, VEC has less vagolytic effects (less increase in heart rate), a moderate increase in potency, higher fat solubility. V_d is 0,4 L/kg, protein bound is intermediate/high (60–80%), plasma clearance ranges from 3 to 6 mL/kg/min, and elimination half-life averages 70 min; the usual duration of action is close to 40 min [5, 7, 8]. Vecuronium i*s 30–40% metabolized by the liver*, renal excretion may account for 30–50%, and hepatic elimination with biliary excretion plays a relatively large role (about 50–60%). In renal failure, the accumulation of the major vecuronium metabolite (*3-desacetilvecuronium*, with 80% of the activity of the parent compound) may be responsible for the prolongation of the NM block, making pivotal the role of neuromuscular monitoring in this setting. In liver failure patients (cholestasis or cirrhosis), increased V_d, decreased clearance, and prolonged elimination half-life increase VEC duration of action in this patient population. Decreased clearance and a consequent prolonged response have been reported in elderly patients, too [5, 7, 8, 10, 18].

The dose required for tracheal intubation ($ED_{95} \times 2$) is 0.1 mg/kg, and provides ideal conditions for intubation in 3–5 min. In the average patient, duration of action ranges from 25 to 50 min. Doses close to $ED_{95} \times 5$ can be used to speed up the muscle paralysis without major cardiovascular effects. Maintenance dose is about 1/10 intubation-dose (0.01–0.015 mg/kg), administered in refracted boluses or by continuous infusion (1–2 μg/kg/min) [7, 8, 18]. Neuromuscular Monitoring (NMM) is strongly advised [5, 15, 17, 20–22]. Maintenance dosages can be reduced by 30–50% if a volatile anesthetic is concomitantly administered [14] and/or readjusted in case of renal failure and in elderly patients. VEC can be antagonized by AChEIs and sugammadex [10, 13–16].

Rocuronium (ROC), an intermediate-acting steroidal agent, has a different chemical structure from vecuronium. Due to this difference, ROC is less potent than VEC (ED_{95} 0.3 mg/kg) and has a more rapid onset [7, 8, 18]. Relevant pK features are small V_d (0.3–0.7 L/kg), an almost negligible protein binding (20%), elimination for the largest part by biliaryroute, renal elimination accounting for only10–20%; the most important metabolite has minor, if any, neuromuscular blocking activity (less than 20% of that of the parent compound). Elimination half-life ranges between 60 and 140 min. It can be antagonized by AChE inhibitors or by sugammadex (as VEC). While in renal failure patients VEC clearance is only marginally affected, in patients with hepatic failure the duration of action may be prolonged due to reduced clearance and increased V_d. Relevant is the impact advanced age may have on VEC metabolism due to increased V_d and decreased clearance [10]. Hemodynamic effects are minimal, there is no vagolytic effect, histamine release is negligible; however,

adverse reactions have been reported [7, 8, 10, 18]. The standard dose for intubation (0.5–0.6 mg/kg, $ED_{95} \times 2$) provides optimal intubating conditions in 1.5–3 min. An increasing dosage (up to 1.2 mg/kg) speeds up the onset of NM block, but increases the duration of action. High-dose ROC is an important alternative in case of rapid sequence induction; in AAs's experience optimal intubating conditions can be recorded in 60–70 s (personal unpublished data). Recent publications have documented the efficacy of 1.2 m/kg rocuronium versus 1.5 mg/kgSCh [23]; the comparable efficacy (even if with slight variability in onset) and the rapid reversal availability (16 mg/kg sugammadex in this specific scenario) [17] make this option of extreme interest and of paramount importance (mainly for safety reasons) in difficult scenarios involving problematic intubation in anesthesia and in ICU patients [7, 8, 17, 18]. Duration of action is of about 30 min, but it can double in case of increased dosage, combination with inhalation agents, or in elderly patients [10]. Usual maintenance dose is 0.1–0.2 mg/kg, to be administered when TOF is 25%; continuous infusion schedule infusion ranges from0.05 to 0.012 mg/kg/min or 0.6–0.72 mg/kg/h [7, 8, 10, 18].

4.4.2 Benzylisoquinoline Derivatives

Mivacurium (rapid onset and short duration of action), *atracurium,* and its isomer *cisatracurium* are available in Italy, the latter being the most utilized agent due to its safety features and ease of use [7, 8, 10, 18].

Atracurium (ATR)—introduced in clinical practice at the beginning of the 1990s, ATR is a bisquaternary ammonium benzylisoquinolinium compound (10 isomers). ED_{95} is 0.2–0.25 mg/kg, duration of action is intermediate, V_d is relatively small (0.15 L/kg). Elimination half-life is rather constant even during continuous infusion (20 min), with a clearance ranging from 4 to 10 mL/kg/min. It was the first NMBA without renal or hepatic metabolism introduced in clinical practice [7, 8, 10, 18]. Due to the relative lack of these two end-stage organ pathway elimination, kinetic parameters and duration of action are relatively unaffected by renal disease or cirrhosis, making the use of ATR attractive in end-organ failure [7, 8, 19]. Its peculiar chemical structure enables degradation both by nonspecific esterase hydrolysis and nonenzymatic pH and temperature-dependent degradation (Hofmann reaction, conversion from quaternary ammonium to tertiary amine amplified by an increase in temperature and by alkalosis). The final product of Hofmann degradation is laudanosine, which has epileptogenic activity in animal models, but not in humans. According to some studies and contrary to the foregoing reported evidence, there is documentation of ester hydrolysis close to 66% and the non-negligible role of the renal elimination [7, 8]. Despite these reported contradictions present in literature, no relevant pharmacokinetic alterations have been documented, also in elderly individuals [10]; a possible explanation could rely upon a constant clearance kept through non–end-organ-dependent pathways [8]. ATR causes histaminergic release, then being prone to hypersensibility and allergic phenomena (tachycardia, hypotension, vasoparalysis). Dose required for intubation is 0.5 mg/kg ($ED_{95} \times 2$)

and ideal conditions for intubation are reached in 2–4 min. Maintenance of a neuromuscular block adequate for surgery (intermediate to deep block) requires additional boluses of 0.1–0.15 mg/kg, or 10–20 μg/kg/min continuous infusion under neuromuscular monitoring andaccording to the type of anesthesia (intravenous vs. volatile); duration of action after the first dose ranges from 30 to 45 min [7, 8, 10, 16, 18]. In fact, recovery of 10% of neuromuscular activity (one twitch in the TOF) takes about 40 min, complete spontaneous recovery up to 60 min [24].

Cisatracurium (CIS)—available in clinical practice since 1995, CIS is the 1R-cis 1′R-cis stereoisomer of ATR. It is three to four times more potent than ATR (ED_{95} 0.05 mg/kg), has intermediate duration of action and, contrary to ATR, does not cause histamine release [7, 8, 16, 18, 19]. Being more potent than ATR, the onset is slower. It is predominantly metabolized by Hofmann reaction (77%), 16% is eliminated by renal pathway making minimal albeit non-negligible the impact of renal failure on clearance rate; in fact, no evidence exists of a prolonged duration of action after bolus dose in renal dysfunction [7, 8, 16, 18]. There are no known active metabolites and V_d does not differ from that of ATR (0.16 L/kg). In liver failure patients, both V_d and clearance are increased, leaving half-life substantially unchanged [7, 8, 16, 18, 19]. Dose for intubation is 0.15–0.2 mg/kg ($ED_{95} \times 4$) with ideal intubation conditions after 4 min. Duration of action after first bolus is about 45–50 min. Absence of histamine release avoids significant circulatory effects. Maintenance requires repeated doses (0.01 mg/kg) or continuous infusion (1–3 μg/kg/min) [7, 8]. It should be stressed that despite longer elimination half-life documented in the geriatric population, recovery from a bolus dose is not affected in this population [10]. NMM is of course always recommended, particularly in "special populations" [5, 20–22].

4.5 Monitoring Neuromuscular Function in Anesthesia [5, 15, 16, 17, 20–22]

In the late 70s, Viby, Mogesen et al. reported that residual neuromuscular block, measured using Train of Four rate (TOF r) <0.7, was present in up to 40% of the patients afterthe use of long-acting NMBA [25]. In more recent reports [26, 27], the incidence of residual neuromuscular blockade (T4/T1 < 90%) was reported to be from 40 to 60%despite the use of intermediate-acting compounds, antagonists, or NMM [27]. Postoperative respiratory complications are quite common after surgery, despite the efforts to understand their causes and reduce their incidence [28–30]. If secondary to residual curarization, postoperative respiratory failure could be extremely severe (life threatening) (0.7 < TOF < 0.9); this is the reason for the frequent and important appointments made by many scientific societies (SIAARTI in March 2018 among the others) [20], for the use of quantitative neuromuscular monitoring (NMM) during surgery and in the immediate postoperative period (including PACU/Recovery Rooms) [5, 15, 17, 20–22, 26–29]. According to a very recent document by SIAARTI (Good Clinical Practice document) [20] and in line with the most recent literature [5, 15, 17, 21, 22, 26–30], the intraoperative *quantitative*

monitoring should be strongly considered to guide the use of NMBAs in case of deep neuromuscular blockade, and in patients affected by end-stage liver failure, kidney failure, neuromuscular disorder. Aim of NMM is to guide the perioperative use of NMBAs, main goals being (1) the optimization of intraoperative drug administration and (2) the postoperative minimization of the risk of residual paralysis. For the latter, mandatory is TOFr >0.9 before extubation [5, 15, 16, 17, 20–22, 26–30]. Even if a large part of the patients with TOFr between 0.7 and 0.9 might not experience adverse respiratory events, the same numbers with high-risk patients (those described earlier) [5] could become problematic and critical.

According to a very recent, comprehensive review by Ortega et al. [10], the main components of NMM are the stimulation of a peripheral nerve and the assessment of the contraction of the innervated muscle; while the electrical stimulation allows a simple *qualitative* assessment (visual or tactile), monitors are able to stimulate, measure, and analyze (*quantitative* assessment) the muscle response to the stimulus. Adequate functional recovery of NM function is then objectively assessed.

Qualitative monitoring is the visual or tactile assessment of the response to peripheral nerve stimulation. ***Quantitative monitoring*** is the direct measure of the force of muscular contraction, translated into values (T4/T1, TOFr) resulting from the ratio between the fourth and the first responses; the result is available on a visual display on a neuromonitoring tool [5, 15, 21].

Assessment modalities of muscular activation following nervous stimulation are [5, 15, 21] *acceleromyography* (the most adopted in clinical practice), *cinemyography, meccanomyography, and electromyography*. A supramaximal current stimulus of 50–60 mA is delivered to adductor pollicis (more common), orbicular or corrugator supercilii muscle (less common); as mentioned earlier, ocular muscles are more resistant to NMBAs than diaphragm, laryngeal muscles, masseter, and adductor pollicis; thus, functional recovery of these muscles occurs well after that of orbicular or corrugator supercilii muscles.

Neuromuscular monitoring after peripheral stimulation is performed using dedicated devices, able to deliver constant currents whose amplitude ranges from 0 to 80 mA. According to Naguib et al. [5], the stimulus should be monophasic, with a square waveform, with a rapid rise and decay. The duration should be minimal (0.3 ms). The frequency of stimulation should be high, but less than 30 Hz, to avoid tetanic response. The amplitude of the threshold current is able to evoke the muscle contraction. While the maximal current determines the contraction of all the fibers in a muscle, the supramaximal current (30% above the amplitude of the maximal current) aims at the contractions of all fibers despite possible changes in resistance; thus, any decrease in the force of muscle contraction is due to the NMBAs effect [5, 15, 22]. Proper skin preparation and correct electrodes placement are mandatory. The ulnar nerve is the most common anatomical site of stimulus to monitor adductor pollicis response; occasionally, according to particular surgical preparations or positioning, flexor hallucis can be an alternative. The temporal branch of facial nerve and supraciliar muscle are sometime used, even if erroneous assessments are possible [5, 10, 15, 16, 22]. The most common stimulating patterns are train of four—stimuli (TOF), post tetanic count (PTC), and single burst (DBS). (see Table 4.1).

4.5.1 Train of Four (TOF) [5, 15, 16, 22]

TOF is the sequence of 4 single twitch electrical impulses (T1-T2-T3-T4) delivered at 2-Hz frequency (1 stimulus every 0.5 s) every 15–20 s. TOF count (TOFc) is the number of responses evoked by the stimulus. The force of muscular contraction, or the depth of the neuromuscular block, in response to the four stimuli ("amplitude" of the response) is provided by T4/T1 ratio (TOFr), calculated by dividing the T4 amplitude by the T1 amplitude. *Fade* (the progressive decrease in response, a phenomenon whose mechanisms are still under investigation) [5] occurs in T3 and T2 between 20% and 10% of single response (T4 less than T1, with the T4 most affected). It is typical with the use of NDNMBAs or in case of phase II block after a very large dose of SCh (>3 mg/kg). In fact, the block induced by SCh causes a progressive reduction in the amplitude of all four twitches (same amplitude, no fade phenomenon, keeping TOFr close to 1). The absence of the first twitch defines the muscular nonresponse to nerve stimulation. During the recovery phase, T1 is the first twitch to recover, T4 can reappear early at 25–30% of single twitch. Hence, all the four responses (twitches) and the TOFr >0.9 are required to rule out any residual muscular blockade and to achieve optimal conditions for safe extubation [5, 15, 16, 20, 26–30]. Ideal conditions for optimal intubation and for specific surgeries are provided in the total absence of muscular response (deep muscular blockade). The average neuromuscular blockade required for surgery is a 1–2 at TOF count. A TOF count of 2 or 3 (SIAARTI recommends more than one twitch) [20] is necessary for the neostigmine administration to antagonize NDNMBAs. On the contrary, sugammadex can antagonize rocuronium and vecuronium at any level of neuromuscular blockade [16, 17, 31]. TOFr >0.9 should be mandatory to accurately confirm complete functional muscular recovery (see also SIAARTI, Good Clinical Practices, and UK recommendations) [20, 30].

4.5.2 Post-Tetanic Twitch Count (PTC) [5, 15, 22]

PTC is the count of the number of muscular responses when a sequence of single-twitch stimulation at 1 Hz for 20 s follows an initial high-frequency stimulation (50 Hz for 5 s, by definition the tetanic stimulation). In normal unparalyzed individuals, the response is a sustained and intensified contraction with no fade. On the contrary, in the presence of NMBAs (or in case of phase II block after high doses of SCh), the response is tetanic fade and post-tetanic potentiation [5, 15]. Progression of recovery from deep blockade using NDNMBAs is characterized by the increase in number and amplitude of PTC. In clinical anesthesia, PTC monitoring could find a place in case of the total absence of TOF responses, as is the case for deep block as is the case during intracranial surgery. According to Baillard [22], the number of responses after tetanus/tetanic stimulation is proportional to the degree of recovery from the blockade. More precisely, according to Naguib et al. [5], PTC can roughly estimate the time needed for the first twitch of TOF while recovering from a deep

block. Interestingly enough, in case of use of intermediate duration NDNMBAs, once PTC approximates 10–12, a TOFc of 1 will appear. A 10 min-interval time is usually required between the first response to PTC and the first twitch at TOF. Adductor pollicis response is used for PTC and a 5-min interval must be observed before repeating evaluation. As evident, tetanic stimulation is painful and should not be applied to the awake individual.

4.5.3 Double-Burst Stimulation (DBS) [5, 15]

DBS, introduced as an alternative to TOF, consists of two short-lasting, 50-Hz tetanic stimuli or bursts separated by a 750-ms interval. It should improve the subjective ability to detect residual NM blockade. Normal response to this pattern of stimulation (no NMBA or complete recovery) involves the comparison of two muscle contractions, higher in amplitude than those evoked by TOF; the second response is less than the first in case of residual nondepolarizing neuromuscular blockade. Generally speaking [5, 15], this pattern of stimulation is considered inadequate to ensure appropriate functional recovery.

4.6 Neuromuscular Blockade Antagonization

Among the many tasks every anesthesiologist has in everyday clinical cases, complete functional neuromuscular recovery after surgery is key, to prevent mortality, morbidity, and complications resulting from PORC [26, 27]. Residual curarization can be ruled out if TOFr >0.9 [5, 15, 20–22, 30], whereas its presence results in muscle weakness, hypoventilation, upper airways obstruction, frequent causes of hypoxic/hypercapnic postoperative complications) [25–29]. Strategies aimed at PORC prevention should include [7, 8, 17, 18, 20, 30]:

1. use of short- or intermediate-action NMBAs,
2. neuromuscular monitoring when NMBAs are used [5]
3. TOF titration of the degree of neuromuscular blockade according to surgical needs: deep block should be if not mandatory for the type of surgery. A major question is nowadays the real necessity of deep block.
4. Assessment of the degree of neuromuscular block at the end of surgery and consequent response.
   (a) TOFr <0.9 >> >Antagonization.
   (b) TOFr >0.9 (=1) no indication for antagonists. It must be noted that residual curarization (TOF < 0.9) may persist in 20–30% for up to 2 h. Thus, the importance of monitoring tools and antagonists administration.
5. ATR or CIS requires neostigmine as an antagonist (appropriate dose ranges between 0.03 and 0.07 mg/kg) to be administered only after TOF count >3. Atropine 0.01 mg/kg is strongly advised.

6. VEC and ROC have a specific antagonist, sugammadex, which can be administered after TOF count >1 (otherwise, wait until TOF count >3 for neostigmine) [31].
7. a recent consensus [16] proposed to wait 15 min before extubation after neostigmine administration with a TOF >3 (or 10 min for a TOF count >4), at the end of sevoflurane-based anesthesia. In case of propofol infusion and TOF count >3, a 5-min interval after neostigmine ensures safe extubation.

Extubation requires TOFr >0.9 after spontaneous resolution of muscle blockade or antagonists action: ACEIs (acetylcholine-esterase inhibitors) are neostigmine, pyridostigmine, edrofonium (the first is still the drug most extensively used in anesthesia and intensive care), and sugammadex, which is the only selective agent capable of steroidal NMBA antagonization [5, 7, 8, 17, 18, 31].

4.6.1 Acetylcholinesterase Inhibitors (ACEIs) [5, 7, 8, 17, 18]

ACEIs increase the amount of ACh at NMJ level; ACh acts as a NMBA competitor on nAChRs restoring muscle activity. Duration of action of neostigmine ranges between 60 and 120 min. Furthermore, ACEIs effects are also directed on muscarinic receptors, potentially leading to clinically relevant parasympaticomimetic effects (mainly bradycardia). Atropine or glycopirrolate must always be available to treat bradycardia. For the (usual) neostigmine dose of 0.03 mg/kg, atropine average dosage is 1 mg. In case of use of glycopyrrolate, 0.2 mg is administered every 1 mg neostigmine. Increased doses may be required if maximum neostigmine doses (0.07 mg/kg, very seldom used, and with relevant possible adverse effects) are used. In case of sevoflurane-based anesthesia and rocuronium as NDNMBA, median reversal time from TOFc 3 to TOFr >0.9 was 15 min (7–43), after neostigmine administration, 9.7 (5.1–7.4) minutes after TOFc >4 and 5 min when propofol was used as the main anesthetic agent. Unavailability of neuromuscular monitoring equipment forces the anesthetist to clinically (subjectively) assess the degree of functional muscular recovery, although this subjective evaluation is prone to errors. It must be emphasized that in case of deep block (PTC >1 TOFc 0) neostigmine is ineffective.

4.6.2 Sugammadex (SUG) [5, 7, 8, 17, 18, 31, 32]

Sugammadex is a modified gamma-cyclodextrin specifically designed to "encapsulate" free-circulating aminosteroidal nondepolarizing muscle relaxants. The highest affinity is documented for rocuronium; SUG does not have any effect on SCh, ATR, or CIS. Free molecules of ROC are "captured" by SUG and free ROC concentration rapidly decreases, creating a gradient between neuromuscular junction and plasma, where they are encapsulated by the gamma-cyclodextrin [17]. Rapid and efficient antagonization results in prompt recovery of neuromuscular transmission. Recovery

of muscle function is significantly more rapid with SUG than neostigmine. SUG dosage must be based on the level/degree of blockade and to the lean/ideal body weight [17]:

1. for deep block (1–2 PTC) 4 mg/kg dose leads to TOF > 0.9 in 5 min,
2. intermediate level of block (TOFc 2–4) 2 mg/kg dose ensures TOFr >0.9 in 3–5 min,
3. in emergency situations (impossible endotracheal intubation, impossible ventilation after muscle paralysis), a dose of 16 mg/kg dose completely reverses muscular blockade in 3 min. Hence, rocuronium at 1.2 mg/kg dose in rapid sequence intubation or in case of complex intubations can be completely, safely, and rapidly reversed.

SUG is not devoid of side effects, including hypersensitivity (5%), anaphylaxys (1:1000–1:20000), and bradycardia [32, 33]. Problematic could be the (re)-use of aminosteroidal agents within a short intermediate period of time after administration. Specifically addressing the problem of reintubation shortly after reversal with SUG, a practical option supported by clinical studies and quoted by Murphy et al. could be the use of rocuronium 1.2 mg/kg, able to produce onset of the neuromuscular block within 3 min (if SUG was administered 5 min before), and within 1.5 min (if SUG was used 30 min before) [17, 32]. Aminosteroidal NDNMBAs should not be used within 5 min of SUG administration (in this specific setting ATR or CIS or SCh should be considered) [32]. Special attention should be reserved for the so-called special populations. In patients suffering from neuromuscular disorders, the use of neostigmine could be problematic because of the risk of muscle weakness. Instead, the use of aminosteroidal compounds reversed by the usual doses of SUG has been successfully reported in many clinical cases; studies in larger series are awaited, but the option has a good rationale [17]. SUG, not recommended in case of severe renal failure, has been successfully used in mild-to-moderate renal dysfunction; in case of severe renal impairment, the ROC-SUG complex is removed by high flux hemodialysis. In case of hepatic dysfunction, the use of SUG was possible; the reversal of neuromuscular block, longer than in healthy patients, was faster and safer than with ACEIs [17]. Kinetic and dynamic profiles are minimally affected in the elderly patient and in the pediatric population [32].

4.7 Future Perspectives [7, 8, 34–36]

New molecules are required to have adequate potency to allow clinically reasonable doses, rapid onset, although this may affect potency, rapid clearance, and metabolism (compatible with potency and rapid onset), with inactivation pathways that are hopefully independent from end-organ function/failure; in other words, a safer profile [32, 34, 35]. According to possible side effects, hemodynamic stability, absence of hypersensitivity/anaphylaxis, and absence of airways alterations are

key. In recent years a very promising compound, *rapacuronium*, was withdrawn from the market in the USA because of interaction with M_2 and M_3 bronchial receptors leading to bronchospasm [34]. **Fumarates** are a new NMBA class that may meet these needs. Among Fumarates, *Gantacurium and CW002* are worth to be mentioned; chloride atom on gantacurium is key to increase the rate of inactivation (degradation) in the presence of L-cysteine, the new essential molecule in reversal of these agents [34, 35]. *Gantacurium* is an ultrashort-acting NMBA, characterized by rapid onset and intermediate potency (ED_{95} 0.19 mg/kg,) being inactivated by hydrolysis; a reaction with L-cysteine can speed up the degradation process. This inactivation mechanism is innovative (spontaneous hydrolysis plus L-cysteine) and occurs in 2–3 min. Ideal conditions for intubation are achieved in 60–90 s using 0.3–0.4 mg/kg (ED_{95} 1.5–2) and could be even shorter using 0.5 mg/kg ($ED_{95} \times 5$). High doses may result in histamine liberation. Blockade antagonization with L-cysteine enables TOF recovery in 2–3 min. Marketing has been hampered by complexity in production operations and side effects [35, 36]. Still under animal experimentation, but promising, seems to be CW 1759–50—a new ultrashort NDBA. Compared to gantacurium, the clinical profile has been defined "superior"; changes in mean arterial pressure and heart rate were less and degradation with L-cysteine very rapid [36].

As recently assessed by Murrel and Savarese [34], the perfect blocking agent, ultrashort acting, provided with the most favorable dynamic and kinetic profiles, with the best safety profile, completely reversible at any time point of blockade and able to offer the same conditions provided by SCh (but devoid of the SCh side effects!) has to be found, as yet. Quite surprisingly, SCh, conceived in 1952, is still the basis of comparison. Promising compounds such as Fumarates and related molecules and L-cysteine reversal are now under intense studies. According to Murrel and Savarese [34], these molecules will have a considerable role in the very next future of our everyday clinical practice.

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