Clinical Pharmacology of Drugs Acting at the Neuromuscular Junction

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Key Points

1. The vertebrate neuromuscular junction is the most studied synapse. Acetylcholine is released from the motor axon terminal, crosses the synaptic cleft, and binds to the recognition sites on the 2 α (alpha) subunits of postsynaptic nicotinic receptors. The generated action potential will result in excitation-contraction coupling.
2. Succinylcholine is an ultra-short acting depolarizing neuromuscular blocking drug (NMBD). It produces the fastest, shortest, and most reliable neuromuscular blockade. Succinylcholine may result in postoperative myalgia, increases in plasma potassium levels that can reach pathologic levels under certain conditions, small increases in intracranial and intraocular pressure, and is one of the known triggers of malignant hyperthermia.
3. Atracurium is a benzylisoquinolinium compound of an intermediate duration composed of 10 isomers and its metabolism occurs independent of renal and hepatic function by Hofmann degradation and plasma esterases hydrolysis. Doses used to facilitate tracheal intubation may be associated with histamine release.
4. Cisatracurium, the *cis-cis* isomer of atracurium (a benzylisoquinolinium compound), is also metabolized by Hofmann degradation. The parent molecule does not undergo ester hydrolysis. Cisatracurium has an intermediate duration. There is virtually no histamine release when compared to its predecessor, atracurium.
5. Mivacurium, another benzylisoquinolinium compound, is a short-acting nondepolarizing NMBD. It is metabolized by butyrylcholinesterase, similar to succinylcholine.
6. Pancuronium is a steroidal, long-acting NMBD that possesses vagolytic and sympathomimetic properties and yields active metabolites (3-OH pancuronium) that increase the incidence of residual neuromuscular blockade. In the modern era of rapid recovery protocols, its use has diminished significantly. The authors do not recommend its use.
7. Vecuronium is a steroidal nondepolarizing NMBD with an intermediate duration of action. It is virtually devoid of hemodynamic effects. However, its degradation into active metabolites precludes its use for prolonged periods in the intensive care unit.
8. Rocuronium is a steroidal nondepolarizing NMBD with an intermediate duration of action. At high doses (1.2 mg/kg or 4 × ED_{95}), it has an onset of action approaching that of succinylcholine.
9. The use of clinical signs such as handgrip strength or sustained head lift, and subjective (visual and tactile) assessment obtained with a peripheral nerve stimulator, are not reliable methods for determining recovery from neuromuscular blockade. Quantitative monitors—using acceleromyography, mechanomyography, or electromyography—are most reliable for excluding residual neuromuscular blockade.
10. Sugammadex is a novel encapsulating reversal agent, capable of rapidly antagonizing any level of rocuronium-induced neuromuscular blockade. Its use, however, does not preclude the need for monitoring the level of neuromuscular blockade, as the appropriate dose is dependent on the level of recovery at the time of its administration.

8.1 Background

Since the first administration of d-tubocurarine in 1942 by Harold Griffith to facilitate muscle relaxation during an appendectomy, neuromuscular blocking drugs (NMBDs) have been a class of medications utilized by anesthesiologists and intensivists to facilitate the performance of invasive and painful procedures. NMBDs are administered to improve the quality of intubating conditions and decrease the incidence of vocal cord injury during airway instrumentation. Furthermore, the use of NMBDs to relax major skeletal muscle groups during intra-cavitary operations significantly improves surgical conditions. The utility of NMBDs is not limited to the perioperative arena; they can be used to facilitate mechanical ventilation in patients with poor pulmonary compliance in the intensive care unit.

Two major classes of NMBDs exist and are distinguished by the manner in which these medications interact with the neuromuscular junction (NMJ) to produce skeletal muscle relaxation. **Depolarizing** drugs act as acetylcholine receptor agonists at the postsynaptic nicotinic receptor. **Nondepolarizing** drugs act as competitive antagonists, as they compete with acetylcholine for the binding sites on the nicotinic acetylcholine receptors at the neuromuscular junction. Nondepolarizing NMBDs can be further subdivided into 2 categories, based on their molecular structures. Aminosteroidal and benzylisoquinolinium (tetrahydroisoquinolines) compounds have distinct structural characteristics that result in substantial differences in the pharmacological profiles of these compounds.

Despite nearly 75 years of experience, studies continue to demonstrate the potential deleterious side effects associated with the use of these medications. In 1954, Beecher and Todd demonstrated a six-fold increase in mortality in patients receiving curare compared with those who had not received curare. Such hazards persist today as the incidence of residual neuromuscular blockade may be as high as 40% of patients in the post-anesthesia care unit (PACU), a complication that leads to increases in pulmonary aspiration events, airway obstruction, attenuation of the hypoxic ventilatory response, and subjective reports of unpleasant weakness-related symptoms. Furthermore, the use of NMBDs has been repeatedly implicated in awareness during surgery when paralyzed patients have inadequate level of anesthesia. Such findings suggest that many clinicians may have an incomplete understanding of the pharmacology of NMBDs, their interactions at the neuromuscular junction, and of the existing techniques to monitor the level of neuromuscular blockade after NMBD administration.

8.2 The Neuromuscular Junction

The corticospinal tracts course in the ventral horns of the spinal cord and contain axons and cell bodies of motor neurons. The axons from this tract exit the spinal cord anteriorly via the ventral root as they course to their destination skeletal muscle groups. The motor unit is the functional contractile unit and is composed of a single myelinated alpha motor neuron and all muscle fibers that receive innervation from this single neuron. A large motor nerve innervates more muscle fibers than a smaller motor nerve does. In general, small motor nerve units innervate the fatigue-resistant "slow" muscle fibers, whereas large motor units innervate the "fast" muscle fibers. Muscles contain a varying mixture of motor units depending on their function. The neuromuscular junction (NMJ) is composed of the presynaptic motor neuron terminal, the postsynaptic muscle surface, and a synaptic cleft (gap) that contains the enzyme acetylcholinesterase. The entire NMJ is capped by terminal Schwann cells.

When an electrical signal courses along the motor nerve to the presynaptic end, depolarization of the neuron occurs at the nerve terminal that opens voltage-gated calcium channels, allowing intracellular calcium concentration to increase, and the subsequent release of acetylcholine (ACh) via exocytosis into the synaptic cleft (Fig. 8.1). ACh then traverses this cleft to reach the postsynaptic junction, where it binds with nicotinic ACh receptors (nAChRs). Approximately 50% of the released acetylcholine is hydrolyzed during the

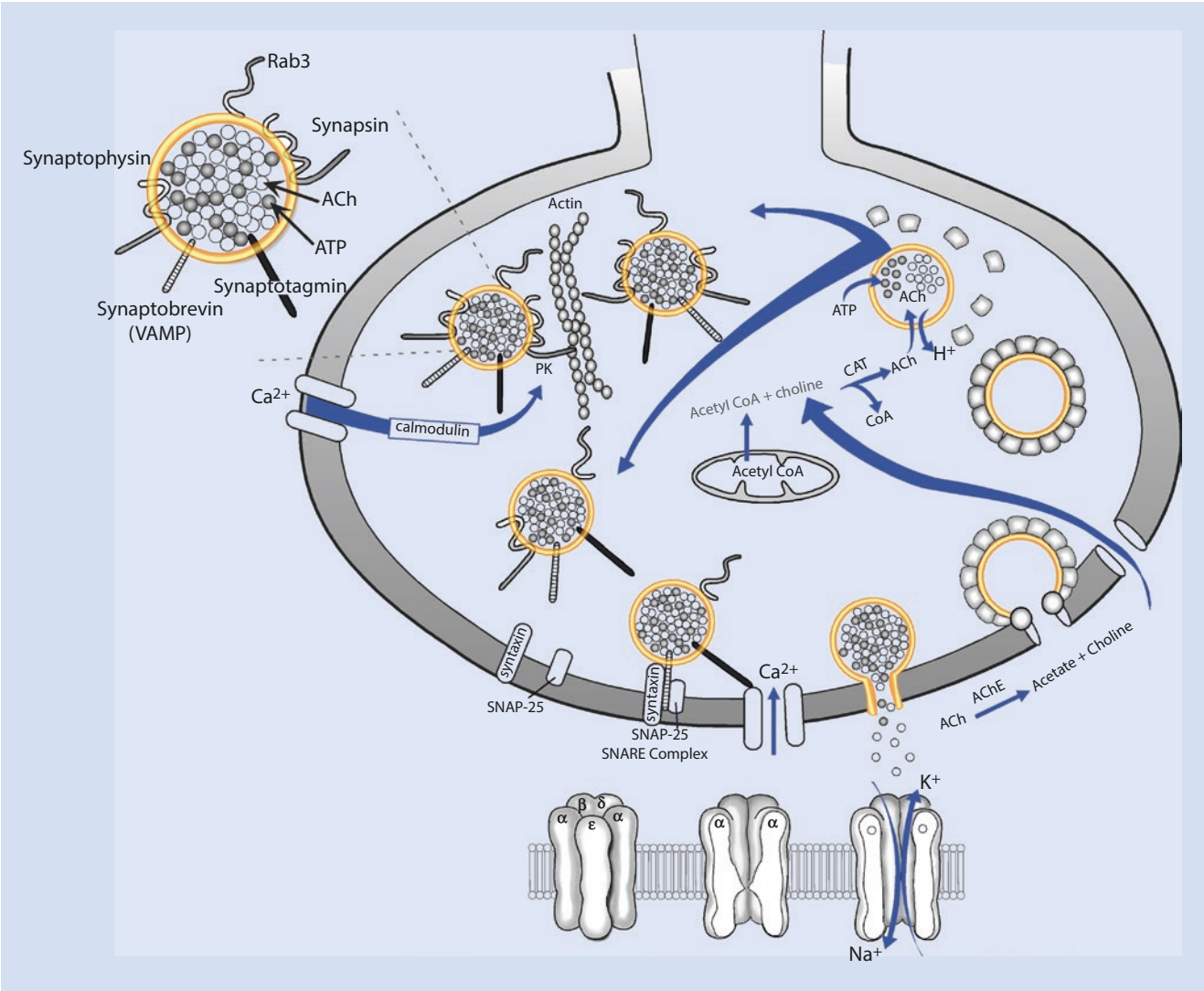

Fig. 8.1 The synaptic vesicle exocytosis–endocytosis cycle. After an action potential and Ca^{2+} influx, phosphorylation of synapsin is activated by calcium-calmodulin activated protein kinases I and II. This results in the mobilization of synaptic vesicles (SVs) from the cytomatrix toward the plasma membrane. The formation of the SNARE complex is an essential step for the docking process. After fusion of SVs with the presynaptic plasma membrane, acetylcholine (*ACh*) is released into the synaptic cleft. Some of the released acetylcholine molecules bind to the nicotinic acetylcholine receptors (nAChRs) on the postsynaptic membrane, while the rest is rapidly hydrolyzed by the acetylcholinesterase (*AChE*) present in the synaptic cleft to choline and acetate. Choline is recycled into the terminal by a high-affinity uptake system, making it available for the resynthesis of acetylcholine. Exocytosis is followed by endocytosis in a process dependent on the formation of a clathrin coat and of action of dynamin. After recovering of SV membrane, the coated vesicle uncoats and another cycle starts again. See text for details. *Acetyl CoA* acetylcoenzyme A, *CAT* choline acetyltransferase, *PK* protein kinase (Reproduced with permission from Naguib et al. [2])

time of diffusion across the synaptic cleft before reaching nAChRs. These nAChRs are concentrated on the folds of the postsynaptic muscle junction, also known as the motor end-plate, with more than 90% of all such receptors located at this junction in adults. When managing patients with electrolyte abnormalities, it is important to remember that hypocalcemia and hypermagnesemia antagonize this release of ACh from the presynaptic motor neuron, leading to a decreased muscle response. In adult skeletal muscle, the postsynaptic nicotinic receptor consists of 5 protein subunits, 2 α(alpha) components and single β(beta),δ(delta), and ε(episolon) subunits (Fig. 8.2).

Once both binding sites on the α(alpha) subunits are bound by 2 ACh molecules or other agonist, a conformational change occurs that opens the ion channel, allowing for the entrance of sodium and calcium and the exit of potassium. The subsequent end-plate potential, when combined with enough other ACh-receptor interactions, depolarizes post-junctional membrane. This depolarization activates voltage-gated sodium channels, which mediate the initiation and propagation of action potentials across the surface of the muscle membrane and into the transverse tubules (T tubules) resulting in the upstroke of the action potential. There are 2 types of calcium channels: the dihydropyridine receptor (DHPR) in the transverse (T) tubules and the ryanodine receptor (RyR1) in the sarcoplasmic reticulum. DHPR-RyR1 interaction releases large amounts of calcium from the sarcoplasmic reticulum, causing muscle contraction. This process is known as excitation-contraction coupling. Repolarization of the muscle membrane is initiated by the closing of the sodium channels and by the opening of potassium ion channel that conducts an outward potassium current. Binding of ACh to only 1 α(alpha) subunit will not result in ion channel opening, current flow through these channels, or membrane depolarization. This scenario may occur in the presence of a nondepolarizing NMBD. Acetylcholine, succinylcholine, and nondepolarizing NMBDs have affinity for the binding sites on the nAChRs.

Fetal nicotinic ACh receptors have a similar pentameric complex (Fig. 8.2), although it contains a δ(delta) rather than an ε(epsilon) subunit, which accounts for its decreased cation conductance and subsequent longer opening time. Clinically, this translates to ACh causing brief activation of these receptors and a reduction in the probability of the channel opening and causing a muscle contraction. This trait makes such fetal receptors resistant to nondepolarizing NMBD and more sensitive to succinylcholine. Furthermore, these receptors increase in denervated states via upregulation,

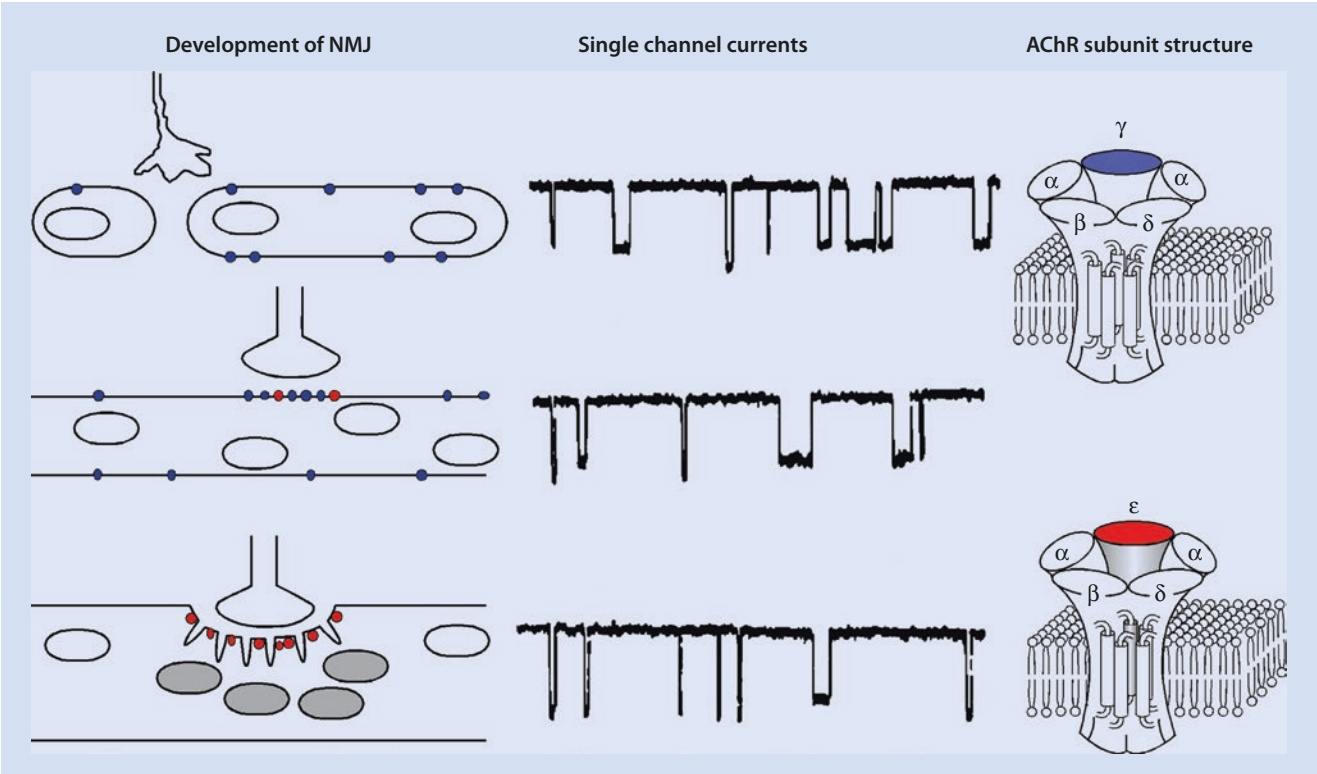

Fig. 8.2 Development of the neuromuscular junction. (*Left*) Motor neuron growth cones contact myotubes as they fuse from myoblasts and express mostly fetal nicotinic acetylcholine receptors (nAChRs; marked in *blue*) in their surface membranes. In adult muscle, adult nAChRs (marked in *red*) predominate and are largely concentrated at the neuromuscular junction. (*Center*) Records of AChR channel openings from muscle membranes at different stages of neuromuscular development. Fetal (*top*) and adult nAChRs (*bottom*) are activated by acetylcholine to form ion channels of different conductance and gating properties. (*Right*) Subunit composition of fetal and adult AChR subtypes. Fetal and adult AChR subtypes are characterized by the presence of a γ(gamma) and ε(epsilon) subunit, respectively (Reproduced with permission from Naguib et al. [2])

when they extend beyond the NMJ (extrajunctional receptors) throughout the muscle membrane. Such upregulation leaves patients vulnerable to exaggerated potassium plasma increases (from intracellular stores) when succinylcholine is administered.

8.3 Depolarizing Neuromuscular Blocking Agents

8.3.1 Succinylcholine

Succinylcholine is the only depolarizing NMBD in clinical use. This compound, also called suxamethonium, is composed of 2 ACh molecules adjoined through an acetate methyl group. This structure accounts for this medication's clinical effects. Succinylcholine produces the fastest, shortest, and most reliable neuromuscular blockade. This is accomplished by activating the postsynaptic ACh nicotinic receptor. Once bound to the both binding sites on the α(alpha) subunits of the nicotinic ACh receptors, hyperpolarization occurs and flaccid paralysis then ensues as the membrane desensitizes. The clinical presentation of fasciculations noted after succinylcholine administration is variable (in location and severity) among patients. It appears that antidromic conduction of action potentials can lead to the activation of unparalyzed parts of the motor unit, resulting in fasciculations.

After an intravenous (IV) bolus of 1–1.5 mg/kg (3–5 × ED_{95}; ED_{95} is the dose that results in 95% depression of twitch height), peripheral muscles become flaccid in 1–2 min, and remain so for 10–12 min. Such a large dose is required as nearly 90% of this compound is hydrolyzed by butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase) in the plasma prior to reaching the NMJ. Despite peripheral muscle paralysis, patients may be able to resume spontaneous breathing as soon as 5 min after administration, as central muscle groups (such as the diaphragm) recover before peripheral groups. As very low concentrations of butyrylcholinesterase exist at the synaptic cleft, the termination of the effect of succinylcholine is determined primarily by its ability to diffuse into plasma (based on its concentration gradient) and the activity of butyrylcholinesterase for its hydrolysis (Table 8.1).

While succinylcholine has many characteristics that make it ideal for facilitating endotracheal intubation, clinicians must be familiar with its ample side effect profile. Most patients experience muscle fasciculation after administration, a clinical sign that foreshadows the ensuing flaccid paralysis, which occurs approximately 1 min after offset of fasciculations. Myalgias are fairly common after succinylcholine exposure, with about half of patients reporting this side effect. While an intuitive causal relationship between uncomfortable-appearing fasciculations and myalgia seems plausible, large-scale reviews have never established such a link. Nonetheless, small "defasciculating" doses of nondepolarizing NMBDs or "self-taming" doses of succinylcholine have been used in an effort to decrease the fasciculations and postoperative myalgia. Such techniques may attenuate myalgia, but have not been found to reliably prevent these side effects; alternatively, such pretreatment may expose patients to risks associated with partial paralysis, such as pulmonary aspiration. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the only evidence-based treatment for succinylcholine-induced postoperative myalgias.

Table 8.1 Pharmacokinetic and pharmacodynamic properties of the depolarizing neuromuscular blocking agent succinylcholine

	Succinylcholine
Class	Depolarizing
Duration	Ultra-short acting
Potency – ED_{95} (mg/kg)	0.25–0.30
Intubating dose (mg/kg)	1.0–1.5
Onset time (min)	1.0–1.5
Clinical duration (min)	7–12
Recovery index (RI_{25-75}) (min)	2–4
Volume of distribution (L/kg)	0.04
Clearance (mL/kg/min)	35
Elimination half-life (min) Normal organ function Renal impairment Hepatic impairment	<1 <1 <1
Maintenance dose (mg/kg)	N/A
Infusion dose (mcg/kg/min)	Titrate to ST muscle response
Elimination route/ metabolism	Butyrylcholinesterase
Active metabolites	No active metabolites
Side effects	Myalgia; bradycardia/ asystole in children or with repeated dosing; dual (phase II) block; anaphylaxis
Contraindications (other than specific allergy)	High K^+; MH; muscular dystrophy; children; receptor up-regulation (e.g., patients with neurologic deficiencies, prolonged immobility; etc.); butyrylcholinesterase deficiency (see text for more details)
Comments	Fastest onset, most reliable NMBD for rapid tracheal intubation

Recovery index (RI_{25-75}) is the time taken for the recovery of the first twitch from 25% to 75% of control twitch height. *ED_{95}* effective dose that produces 95% depression of twitch height. The intubating dose for succinylcholine is ~3xED_{95} dose, *NMBD* neuromuscular blocking drug, *K^+* potassium, *MH* malignant hyperthermia

Table 8.2 Relationship between dibucaine number and duration of succinylcholine or mivacurium neuromuscular block

Type of butyrylcholinesterase	Genotype	Incidence	Dibucaine number[a]	Response to succinylcholine or mivacurium
Homozygous typical	$E_1^uE_1^u$	Normal	70–80	Normal
Heterozygous atypical	$E_1^uE_1^a$	1/480	50–60	Lengthened by 50–100%
Homozygous atypical	$E_1^aE_1^a$	1/3200	20–30	Prolonged to 4–8 h

[a]The dibucaine number indicates the percentage of enzyme inhibited

Again, owing to its similar structure to ACh, succinylcholine can produce bradycardia and even asystole, particularly in children or after repeated doses. In pediatrics, co-administration with atropine is a common practice to maintain the heart rate and subsequently, cardiac output, in the pediatric patients with fixed stroke volumes.

Succinylcholine causes a reliable increase in the plasma potassium level (0.5 mEq/L) in otherwise healthy patients. This side effect has little clinical importance unless patients have pre-existing hyperkalemia. Renal failure patients are no more susceptible to an exaggerated response to succinylcholine than are those with normal renal function. Alternatively, an exaggerated potassium increase that may lead to cardiac arrhythmia and even arrest can occur in patients with conditions associated with upregulation of extra junctional nicotinic nAChRs. As previously mentioned, such upregulation occurs in chronic denervated states, seen in patients with neuromuscular disease, massive trauma, sepsis, prolonged immobility or burns.

Succinylcholine is also associated with increases in intragastric pressure; however, proportional increases in the lower esophageal sphincter tone negate the potential risk of regurgitation. Transient increases in intraocular pressure also occur (up to 15 mm Hg) by unclear mechanisms. While this small increase in pressure must be considered and avoided in patients with preexisting high intraocular pressure, inadequate anesthesia, coughing, and ventilator dyssynchrony produce much greater increases in intraocular pressure. Co-administration with lidocaine or sufentanil can be used to attenuate succinylcholine-induced increases in intracranial pressure. Small increases in intracranial pressure also occur after succinylcholine administration; however, inadequate anesthesia during laryngoscopy with a subsequent hypertensive response is much more likely to elevate intracranial pressure.

The United States Food and Drug Administration (FDA) has issued a "black box" warning for succinylcholine in pediatrics, as these patients may have an undiagnosed myotonia or muscle dystrophy. Succinylcholine may trigger rhabdomyolysis and a fatal hyperkalemic state in these patients. Furthermore, succinylcholine is contraindicated in patients with malignant hyperthermia, a risk that is significantly increased when volatile anesthetics are used. Masseter muscle spasm is another complication that is specific to succinylcholine administration and may be associated with malignant hyperthermia.

The use of succinylcholine is also contraindicated in patients with butyrylcholinesterase deficiency (Table 8.2). The heterozygous deficient state is present in approximately 1 in 480 patients, while the homozygous version may be present in 1 in 3,200 individuals. These patients require a much longer time to recover from succinylcholine administration and may require unanticipated postoperative mechanical ventilation and sedation/amnesia as they recover.

8.4 Nondepolarizing Neuromuscular Blocking Agents

Nondepolarizing NMBDs act as competitive antagonists by binding to the α(alpha) subunits of the nicotinic acetylcholine receptor. NMBDs have been classically classified either based on their duration of action (long-, intermediate, and short-acting agents) or based on their structure (steroids or benzylisoquinolinium) (Table 8.3 and Table 8.4). Nondepolarizing NMBDs are positively charged, relatively large molecules. In general, a dose of 2–3 × ED_{95} is used to facilitate tracheal intubation while a dose of 10% of the ED_{95} is used to maintain neuromuscular blockade (Fig. 8.3).

8.4.1 Benzylisoquinolinium Compounds

Atracurium is a bis-benzylisoquinolinium compound that is mixture of 10 isomers. The ED_{95} is 0.2 mg/kg, with an intubating dose 0.5 mg/kg that yields suitable laryngoscopy conditions after 2.5–4.0 min. This intermediate-duration nondepolarizing NMBA lasts 30–45 min after administration of an intubating dose. Atracurium is metabolized through 2 distinct pathways that are almost completely independent of renal and hepatic function: a nonenzymatic degradation (called Hofmann elimination) and hydrolysis by nonspecific plasma esterases. Hofmann elimination is a pH- and temperature-dependent reaction in which higher pH and temperature favor elimination. Atracurium is relatively stable at pH 3.0 and 4 °C and becomes unstable when injected into the bloodstream. Doses exceeding 0.5 mg/kg are associated with histamine release that can result in flushing, tachycardia, and hypotension. One breakdown product from Hofmann elimination, laudanosine, has been implicated in a theoretical risk of increased central nervous system excitability; however, at clinically relevant doses such complications have not been reported.

Table 8.3 Pharmacokinetic and pharmacodynamic properties of benzylisoquinolinium nondepolarizing neuromuscular blocking agents

	Mivacurium	Atracurium	Cisatracurium
Class	Non-depolarizing	Non-depolarizing	Non-depolarizing
Duration	Short	Intermediate	Intermediate
Potency – ED_{95} (mg/kg)	0.08	0.25	0.05
Intubation dose (mg/kg)	0.2	0.5	0.15–0.20
Onset time (min)	3–4	3–5	4–7
Clinical duration (min)	15–20	30–45	35–50
*Recovery index (RI_{25-75}) (min)	7–9	10–15	12–15
Volume of distribution (L/kg)	~0.2 for the 3 isomers	~0.15	~0.16
Clearance (mL/kg/min)	30–45	5.3–6.6	5.7
Elimination half-life (min) Normal organ function Renal impairment Hepatic impairment	2–2.5 3–4 3–6	21 21 21	23–30 Mild increase 23–30
Maintenance dose (mg/kg)	0.1	0.1	0.01
Infusion dose (mcg/kg/min)	5–8	10–20	1–3
Elimination route	Plasma cholinesterase (70% of succinylcholine rate)	Renal 10%; Hofman elimination 30%; ester hydrolysis 60%	Hofman elimination. No ester hydrolysis of the parent molecule
Active metabolites	No active metabolites	No active metabolites. Laudanosine and acrylates metabolite	No active metabolites. Laudanosine and monoquaternary acrylate metabolite
Side effects	Histamine release	Histamine release	
Contraindications (other than specific allergy)	Butyrylcholinesterase deficiency	Hemodynamically unstable patients due to histamine release	None
Comments	Composed of 3 isomers (*cis-trans, trans-trans and cis-cis*). Reversal by cholinesterase inhibitors; edrophonium for antagonism more effective during deep block	It is composed of 10 isomers. Organ-independent elimination	Cisatracurium is the *cis–cis* isomer of atracurium, accounting for 50% in terms of neuromuscular blocking activity of atracurium. It is approximately 4 times as potent as atracurium but does not cause histamine release. Minimal plasma laudanosine and acrylate levels

The data are averages obtained from published literature, assume there is no potentiation from other co-administered drugs (such as volatile inhalational anesthetics), and the effects are measured at the adductor pollicis muscle. Other factors, such as muscle temperature, mode of evoked response monitoring, type/site of muscle monitoring, etc. will affect the data. ED_{95} effective dose that produces 95% depression of twitch height. The intubating dose for nondepolarizing neuromuscular blocking drugs is traditionally $2xED_{95}$ dose. Recovery index (RI_{25-75}) is the time taken for the recovery of the first twitch from 25% to 75% of control twitch height. This requires the use of a quantitative monitor and stabilization and calibration of the baseline twitch response before the administration of neuromuscular blocking drugs

Table 8.4 Pharmacokinetic and pharmacodynamic properties of aminosteroid nondepolarizing neuromuscular blocking agents

	Vecuronium	Rocuronium	Pancuronium
Class	Non-depolarizing	Non-depolarizing	Non-depolarizing
Duration	Intermediate	Intermediate	Long
Potency – ED_{95} (mg/kg)	0.05	0.3	0.07
Intubating dose (mg/kg)	0.1	0.6	0.1
Onset time (min)	3–4	1.5–3	3–5
Clinical duration (min)	25–50	30–70	60–120
Recovery index (RI_{25-75}) (min)	10–25	8–13	30–45
Volume of distribution (L/kg)	0.4	0.3–0.7	0.2–0.3
Clearance (mL/kg/min)	5	10	1.8
Elimination half-life (min) Normal organ function Renal impairment Hepatic impairment	65–75 Mild increase Significant increase	100–250 100–300 120–400	90–160 Increased x2 Increased x2
Maintenance dose (mg/kg)	0.01	0.1	0.02
Infusion dose (mcg/kg/min)	1–2	5–12	20–40 (not recommended)
Elimination route	Renal 10–50%; Hepatic 30–50%	Hepatic 90%; Renal 10%	Renal 40–70%; Hepatic 20%
Active metabolites	3-desacetyl-vecuronium	17-desacetyl-rocuronium (minimal)	3-OH-pancuronium; 17-OH-pancuronium
Side effects	Vagal blockade with large doses	Minimal	Vagal block (tachycardia), catecholamine release
Contraindications (other than specific allergy)	None	None	Short surgical procedures (< 60 min); not recommended for continuous infusion
Comments	In patients in the ICU who have renal failure, 3-desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade; elimination half-life halved in late pregnancy; 3-desacetyl metabolite has 60% of the parent compound potency	Rocuronium is approximately 6–10 times less potent than pancuronium and vecuronium, respectively. Elimination half-life prolonged in ICU patient; 17-desacetyl metabolite has 20% activity	Significant accumulation, prone to residual block (3-OH metabolite has 50% activity of pancuronium); total clearance is delayed, and the duration of action is significantly lengthened by severe disorders of renal or hepatic function

The data are averages obtained from published literature, assume there is no potentiation from other co-administered drugs (such as volatile inhalational anesthetics), and the effects are measured at the adductor pollicis muscle. Other factors, such as muscle temperature, mode of evoked response monitoring, type/site of muscle monitoring, etc. will affect the data. *ED_{95}* effective dose that produces 95% depression of twitch height. The intubating dose for nondepolarizing neuromuscular blocking drugs is traditionally $2xED_{95}$ dose. Recovery index (RI_{25-75}) is the time taken for the recovery of the first twitch from 25% to 75% of control twitch height. This requires the use of a quantitative monitor and stabilization and calibration of the baseline twitch response before the administration of neuromuscular blocking drugs. *ICU* intensive care unit

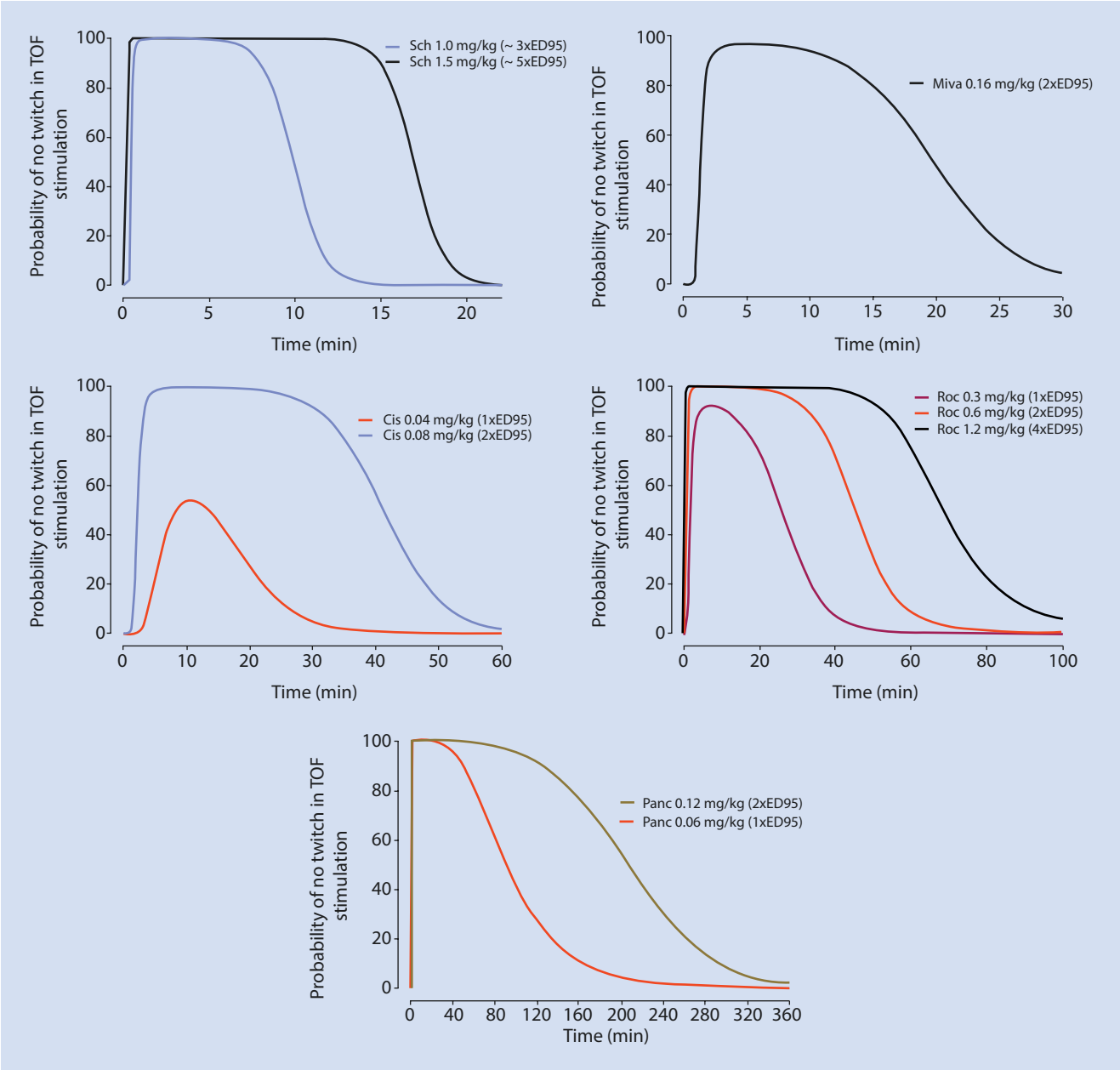

Fig. 8.3 Probability of no-twitch response to train-of-four (TOF) stimulation over time resulting from administration of different ED_{95} (the dose that results in 95% depression of twitch height) doses of different neuromuscular blocking drugs. *Sch* succinylcholine, *Miva* mivacurium, *Cis* cisatracurium, *Roc* rocuronium, Pancpancuronium

Cisatracurium is the *cis*-isomer of atracurium and represents about 15% of the marketed atracurium mixture by weight, but accounts for more than 50% in terms of potency or neuromuscular blocking activity. It is approximately 4 times more potent than atracurium with an ED_{95} of 0.05 mg/kg and, unlike atracurium, it does not cause histamine release in the clinical dose range. The administration of $2 \times ED_{95}$ of cisatracurium provides intubating conditions in about 3–5 min. Like atracurium, it is broken down by Hofmann elimination, but there is no ester hydrolysis of the parent molecule. Its organ-independent elimination pathway, combined with its hemodynamic stability and lack of associated histamine release make this NMBD ideal for use in the intensive care unit (ICU). The incidence of anaphylaxis from both cisatracurium and atracurium is lower than that of rocuronium and succinylcholine.

Mivacurium was developed in an effort to combine the safety profile of nondepolarizing NMBD with the rapid onset and short duration of action of depolarizing drugs. Its structure is similar to that of atracurium, save for an additional methylated phenolic group. It consists of 3 stereoisomers, with the trans-trans and *cis*-trans isomers accounting for the majority of its neuromuscular blocking activity. Like succinylcholine, it is metabolized by butyrylcholinesterases (with 75% efficiency), and therefore has a slightly longer duration of action (15–20 min). Like succinylcholine, mivacurium

should not be used in patients with butyrylcholinesterase deficiency. With an ED_{95} of 0.08 mg/kg, 3–4 times this dose is needed for achieving intubating conditions reliably. Such doses, however, may result in significant histamine release and ideal intubating conditions are still not achieved for 2 min or longer. These limitations have prevented its widespread use in the US, although efforts are currently being made to re-introduce this agent to the market.

8.4.2 Steroidal Compounds

Pancuronium is a long-acting nondepolarizing NMBD with several clinical features of interest. It possesses vagolytic effects, as well as direct sympathomimetic stimulation as it blocks the reuptake of norepinephrine. The ED_{95} is 0.07 mg/kg and a dose of 0.1 mg/kg will provide intubating conditions within 3–4 min. Recovery from such a dose, defined as time from injection until recovery of twitch height to 25% of control (clinical duration), takes nearly 90 min. This prolonged duration of action is at least partially due to the accumulation of an active metabolite, 3-OH pancuronium, following pancuronium's hepatic metabolism. The majority of pancuronium (85%) is eliminated renally, with the remainder being excreted by the liver. Given its prolonged effect and the concern for postoperative residual paralysis and associated morbidity, many clinicians elect to use other NMBD when trying to achieve neuromuscular blockade in their patients.

Vecuronium is an intermediate-acting nondepolarizing NMBD that produces paralysis with minimal hemodynamic effects. Its ED_{95} is 0.05 mg/kg and an intubating dose ($2 \times ED_{95}$) results in adequate conditions within 3 min. Such a dose results in a 45–90 min recovery time. Specific to vecuronium are its various metabolites, one of which (3-OH vecuronium) has 60% potency relative to the parent compound. Like pancuronium, such metabolites are generated from hepatic metabolism and vecuronium is eliminated mostly (60%) through biliary excretion, with the remainder being removed renally. These features preclude its safe use in the intensive care unit where repeated doses can lead to accumulation and prolonged duration of action, leading to critical illness polyneuromyopathy (CIPM).

Rocuronium is also an intermediate-acting nondepolarizing NMBD that can be used for rapid sequence induction and intubation as its onset of action time approaches that of succinylcholine when a dose of 1.2 mg/kg is used. Its ED_{95} is 0.3 mg/kg and the duration of recovery from an intubating dose is similar to that of vecuronium. Also, like vecuronium, it has a stable hemodynamic profile with no associated release of histamine. Rocuronium does not generate clinically relevant metabolites. While spontaneous recovery from a rapid sequence induction and intubating dose is much longer for rocuronium than for succinylcholine, the availability of sugammadex has allowed for a greater safety profile when using rocuronium. The incidence of anaphylaxis from any neuromuscular blocker is as high as 1 in 6500 administrations in some countries, and rocuronium (and succinylcholine) have the highest incidence of NMBD-induced anaphylaxis. Rocuronium is excreted unchanged through both biliary (~70%) and renal (~30%) mechanisms.

8.5 Drug Interactions

8.5.1 Mechanisms of Drug Interactions

Pharmacokinetic interactions are interactions in which one drug alters the rate or amount of absorption, distribution, metabolism, or excretion of another drug (or any combination of these processes). Pharmacodynamic interactions occur when the dose-response relationship of a drug is altered by the co-administration of a second drug. These interactions are generally described as being synergistic, antagonistic, or additive.

The interaction between succinylcholine and NMBDs depends on the order of administration and the doses used. Administration of small doses of different NMBDs before succinylcholine to prevent fasciculations has an antagonistic effect on development of the subsequent depolarizing block produced by succinylcholine. Therefore, it is recommended that the dose of succinylcholine be increased after the administration of a defasciculating dose of a NMBD. In contrast, the administration of succinylcholine before NMBDs appears to potentiate the effects of nondepolarizing NMBDs.

In an era of polypharmacy, anesthesiologists must be aware of the various drug interactions that may occur with NMBD use. For instance, inhalational anesthetics potentiate neuromuscular blockade, likely by affecting post-junctional receptors. This response depends not only on the type of such volatile anesthetics (desflurane > sevoflurane > isoflurane), but also the concentration and duration of exposure. Local anesthetics are another commonly utilized class of medications in the operating room that interact with NMBDs. These medications have the potential to prolong the duration of action of both depolarizing and nondepolarizing NMBDs. Certain antibiotics, such as streptomycin and neomycin, have been found to prolong the response to NMBD as well, although newer antibiotics have not been implicated. Magnesium, a medication commonly used when treating obstetric patients with eclampsia, prolongs the normal response to neuromuscular blockade by preventing the release of acetylcholine from the presynaptic terminal. Similarly, patients receiving chronic lithium can have a prolonged response to both depolarizing and nondepolarizing NMBD as this medication inhibits presynaptic neuromuscular transmission and postsynaptic muscle contraction.

Antiepileptic drugs have a significant impact on the response to NMBD administration. Patients taking antiepileptic drugs chronically have a relative resistance to aminosteroidal nondepolarizing NMBDs and may require more frequent dosing during maintenance of neuromuscular blockade. However, acute administration of antiepileptic drugs is associated with a prolonged response to NMBD.

8.6 Reversal Drugs (NMBD Antagonists)

Traditionally, reversal of neuromuscular blockade has been achieved through the administration of acetylcholinesterase inhibitors. These medications inhibit the breakdown of ACh, causing an increase in ACh relative to nondepolarizing NMBD at the nicotinic ACh receptor. By more effectively competing with NMBDs for nAChR binding sites, ACh results in the generation of normal transmission and subsequent muscle contraction. Three acetylcholinesterase inhibitors are available today: edrophonium, neostigmine, and pyridostigmine. The latter of these medications has the longest onset of action, longest duration of action, and possesses central effects as its tertiary amine structure allows it to traverse the blood-brain barrier. As such, pyridostigmine is not utilized in the operating arena; rather, it is utilized to treat weakness associated with myasthenia gravis.

Neostigmine is currently the most frequently used acetylcholinesterase inhibitor. As with all acetylcholinesterase inhibitors, neostigmine has significant parasympathomimetic effects as ACh interacts with cholinergic receptors throughout the body. For instance, these agents cause a pronounced bradycardia and other bradyarrhythmias as well as bronchoconstriction through muscarinic receptor activation. In order to mitigate these effects, anti-muscarinic agents are co-administered with acetylcholinesterase inhibitors. Glycopyrrolate is typically administered with neostigmine, and atropine is administered with edrophonium, as these pairings reflect similar onset times between the 2 classes of medications. The dose of neostigmine must be guided by the level of neuromuscular blockade: acetylcholinesterase inhibitors are ineffective at reversing deep levels of neuromuscular blockade when train-of-four (TOF) count is zero and only post-tetanic twitches are present. At the other extreme, administration of neostigmine once recovery is almost complete may have the paradoxical effect of inducing muscle weakness. Therefore, reversal with neostigmine should occur at moderate-to-shallow levels of neuromuscular blockade (TOF count of 2–4 with muscle fatigue or fade).

In addition to considering the depth of neuromuscular blockade, several other factors must be considered when utilizing acetylcholinesterase inhibitors for reversing NMBD-induced paralysis. As previously discussed, neuromuscular blockade can be potentiated by a variety of factors such as volatile anesthetics, aminoglycoside antibiotics, hypercarbia, acidosis, hypothermia, hypocalcemia, or hypermagnesemia. The type of nondepolarizing NMBD also affects recovery from neostigmine reversal, as recovery from long-acting agents such as pancuronium is prolonged when compared to recovery from intermediate-acting NMBD. The elderly population also has slower recovery following neostigmine reversal. Such confounding factors, combined with the fact that patients respond in a heterogeneous manner to both NMBD and pharmacologic reversal with acetylcholinesterases, may partly explain the high incidence of residual neuromuscular blockade, particularly when quantitative monitoring is not employed by clinicians.

Edrophonium is an acetylcholinesterase inhibitor with a faster peak onset of action time than neostigmine: 1–2 min vs. 7–11 min, respectively. As a result of ionic bonds that it forms with the acetylcholinesterase enzyme, rather than the stronger covalent bonds of neostigmine, edrophonium has less affinity for this enzyme and therefore should only be used to antagonize shallow levels of blockade. The typical antagonist dose is 0.5–1.0 mg/kg. Given its fast onset time, atropine is co-administered with edrophonium.

8.7 Selective Relaxant Binding Agents

Sugammadex is a modified gamma-cyclodextrin compound composed of an 8-membered ring with a central cavity that encapsulates steroidal NMBDs. This modification entails: (1) the addition of 8 side chains to extend the cavity of gamma-cyclodextrin in order to better accommodate the 4 hydrophobic steroidal rings of rocuronium; and (2) the inclusion of negatively charged carboxyl groups at the end of the side chains in order to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium. Sugammadex exerts its effect by forming very tight complexes at a 1:1 ratio with steroidal NMBDs (rocuronium > vecuronium > > pancuronium). Sugammadex has little to no affinity for binding to benzylisoquinolinium neuromuscular blockers or to succinylcholine. The intravenous administration of sugammadex rapidly binds all available unbound (free) rocuronium molecules, creating a concentration gradient that favors the movement of steroidal NMBD molecules from the NMJ back into the plasma. This removal of NMBD from the NMJ results in a fast recovery of neuromuscular function, as ACh no longer has to compete with the NMBA for the receptor sites. The sugammadex-steroidal NMBD moiety is excreted in the urine. Sugammadex, therefore, acts as a binding agent and has no effect on acetylcholinesterase or any receptor system in the body. Such reversal is devoid of the various side effects associated with acetylcholinesterase inhibition.

At doses of 2 mg/kg, sugammadex reverses rocuronium and vecuronium when the TOF count is at least 2 in about 3 min. A dose of 4 mg/kg is recommended for antagonism of deeper levels of blockade (such as when only post-tetanic twitches are present). A dose of 16 mg/kg can be used to rapidly and emergently reverse the effects of 1.2 mg/kg

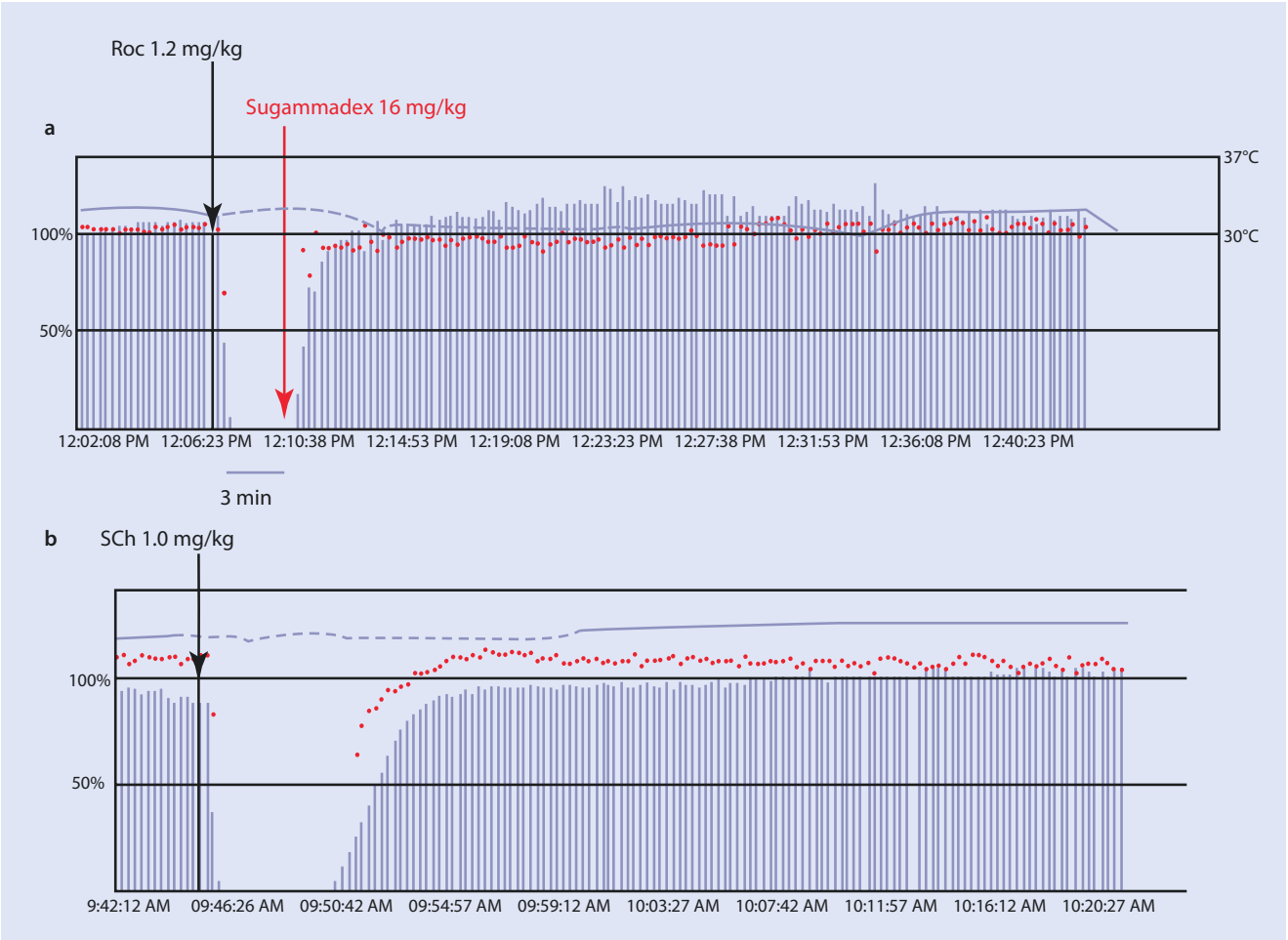

Fig. 8.4 *Panel A* shows the recovery of the twitch height and train-of-four (TOF) ratio after administration of 1.2 mg/kg rocuronium followed 3 min later by 16 mg/kg sugammadex, both given IV. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 s later. The onset-offset time with this sequence (i.e., the time from the end of the injection of rocuronium to a T1 recovery to 90%) was 4 min 47 s. *Panel B* shows the effects of administering 1.0 mg/kg succinylcholine (SCh) with spontaneous recovery to a T1 of 90% occurring after 9 min and 23 s (Reproduced with permission from Naguib et al. [16])

rocuronium. This dose of sugammadex restores muscle function faster than the spontaneous recovery from succinylcholine administration (Fig. 8.4). However, pharmacologic intervention with sugammadex should not be relied upon to rescue patients in the setting of "cannot intubate, cannot ventilate" (CICV) crisis (Fig. 8.5). Following induction of anesthesia, rescue reversal of 1.2 mg/kg rocuronium with 16 mg/kg sugammadex in the setting of CICV may still not result in reliable, immediate return of spontaneous ventilation. In a simulation study, it was reported that, in obese and morbidly obese patients, even after adequate preoxygenation, neuromuscular reversal may not be sufficiently rapid to prevent significant hemoglobin desaturation. The clinical management of CICV should primarily focus on restoration of airway patency, oxygenation, and ventilation consistent with the American Society of Anesthesiologist's *Practice Guidelines for Management of the Difficult Airway* [1].

There are several patient factors that must be considered when utilizing this reversal agent. First, this drug binds oral contraceptive medications and patients receiving this medication should be advised to utilize alternative birth control means for the week succeeding its administration. As previously stated, sugammadex is cleared renally, but it can also be removed via high-flux hemodialysis. Reestablishing neuromuscular blockade after sugammadex reversal should involve the use of benzylisoquinolinium compounds—although case reports have documented the successful use of higher doses of rocuronium after sugammadex. As with any medication, hypersensitivity reactions can occur, with an estimated incidence between 1:3,500 and 1:20,000. Such reactions typically occur within the first 4 min after sugammadex administration, and the subsequent cardiovascular collapse has been successfully treated with epinephrine and volume resuscitation.

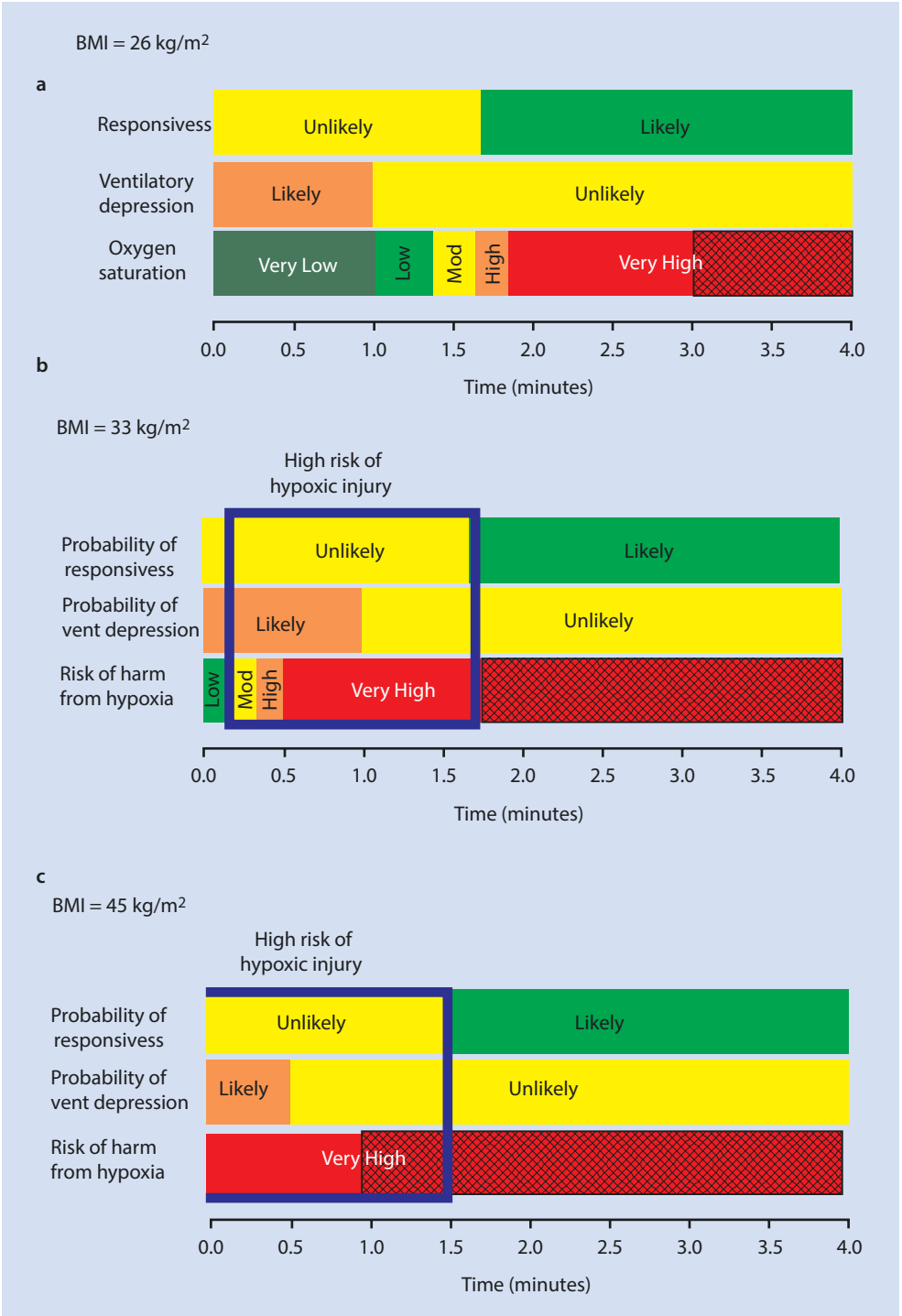

Fig. 8.5 Comparison of responsiveness, intolerable ventilatory depression, and hypoxia to estimate periods of *high risk of hypoxic injury* after induction with failure to ventilate or secure the airway. For discussion purposes, the duration of effects presented in this table are presented as the time from reversal of rocuronium neuromuscular blockade with sugammadex (*vertical pink line* in **c**) until selected endpoints in drug effects. See methods for criteria used to estimate a high risk of hypoxic injury. **a** and **b** present the definitions of the scales used to characterize the probability of effects. Time segments that met criteria are identified with a *blue rectangle*. The *blue rectangle* for the BMI of 45 kg/m^2 is truncated at time = 0 min because criteria were met for a high risk of injury 1.5 min before reversal with sugammadex (Reproduced with permission from Naguib et al. [21])

8.8 Neuromuscular Blockade Monitoring

8.8.1 Clinical Testing

Prior to the widespread availability of peripheral nerve stimulators and quantitative neuromuscular blockade monitors, clinicians relied on various clinical tests to assess adequate recovery from neuromuscular blockade. Such tests include assessing vital capacity, negative inspiratory force, and tidal volume during spontaneous ventilation in the intubated patient. Clinicians have also assessed recovery through testing grip strength and the performance of a 5-s head lift. Despite such widespread practice, all clinical signs of recovery such as the ventilatory parameters or the ability of a patient to lift the head or sustain a handgrip for 5 s, are inaccurate and insensitive for detecting residual neuromuscular

block. Whatever clinical test is employed, residual paralysis, defined as a train-of-four (TOF, or T_4/T_1) ratio less than 0.9, is as high as 40% in the recovery room when subjective monitoring is used intraoperatively. Residual postoperative paralysis has numerous associated complications such as upper airway obstruction, aspiration, and hypoxemia. When such patients require unplanned re-intubation and intensive care admission, mortality increases significantly.

8.8.2 Subjective Evaluation

The use of a peripheral nerve stimulator (PNS) allows for the subjective monitoring of the level of neuromuscular blockade. This monitoring modality utilizes stimulating skin electrodes placed on the skin overlying a superficial motor nerve that innervates the muscle of interest. The negative (typically black) electrode is placed distally to the positive (typically red) electrode (Figs. 8.6 and 8.7). Subjective assessment consists of evaluating and comparing the strength of sequential evoked muscle responses.

Peripheral nerve stimulators have been used clinically for more than 6 decades and typically involve delivering a train-of-four stimulation pattern in which 4 successive single twitch stimuli are delivered at 2 Hz. The degree of fade is then determined by estimating the TOF ratio, which compares the amplitude of the fourth twitch (T_4) to that of the first twitch (T_1). In addition to monitoring recovery, performing a TOF stimulus pattern allows monitoring the degree of nondepolarizing NMBD-induced paralysis, as the TOF count correlates with the percent of post-synaptic nicotinic ACh receptors occupied by nondepolarizing NMBD. Presence of 1 of 4 twitches (TOF count = 1) correlates with more than 95% of such receptors being blocked. Two twitches (TOF count = 2) correlates with 85–90% occupancy. Presence of 3 twitches (TOF Count = 3) corresponds with 80–85% receptor occupancy. Presence of all 4 twitches after TOF stimulation suggests that 70–75% of receptors are blocked. Subjective evaluation of TOF stimulation with the use of a PNS requires the observer to determine the number of twitches and the strength of the first response in the train and compare it to the fourth evoked response by tactile or visual means. The major limitation of evaluating the TOF ratio subjectively is that once TOF ratio approaches 0.40, most clinicians cannot detect the presence of fade. This failure underscores that subjective assessment is unreliable at determining recovery from neuromuscular blockade and exposes patients to the avoidable risks associated with residual neuromuscular weakness. The authors recommend the use of objective monitoring whenever possible.

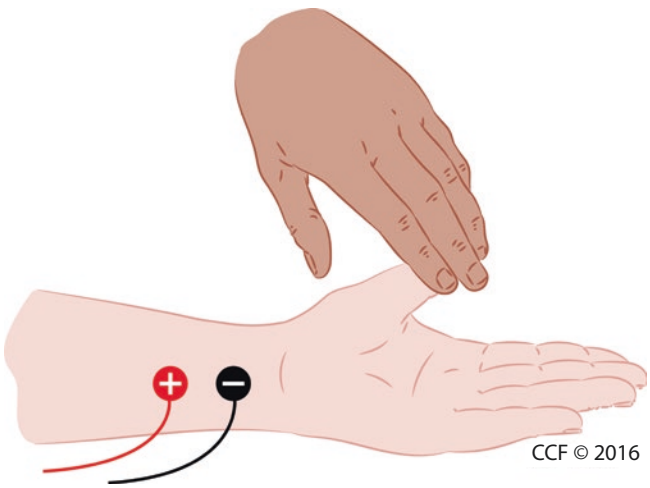

Fig. 8.6 Subjective (tactile) evaluation of neuromuscular responses at the adductor pollicis (thumb) muscle in response to ulnar nerve stimulation. Note that the *black* (*negative*) electrode is distal to the proximal, *red* (*positive*) electrode (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

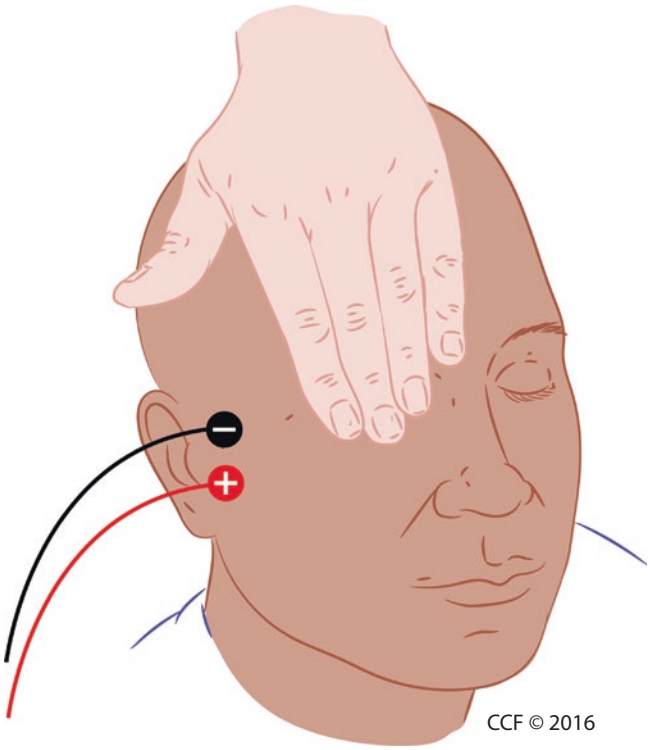

Fig. 8.7 Subjective (tactile) evaluation of neuromuscular responses at the orbicularis oculi (eye) muscle in response to facial nerve stimulation. Note the *negative* (*black*) electrode is placed distally (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

8.8.3 Objective Evaluation

Objective evaluation involves the quantification of the TOF ratio through the measurement of electrical or mechanical response to nerve stimulation. There are numerous modalities

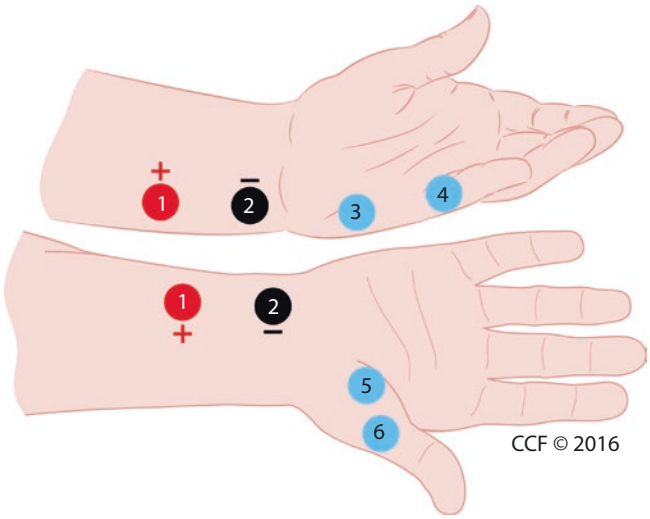

Fig. 8.8 Placement of the stimulating electrodes (*1* and *2*) along the ulnar nerve; and of the recording electrodes for monitoring the abductor digiti minimi (*3* and *4*) or the adductor pollicis (*5* and *6*) muscles by electromyography (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

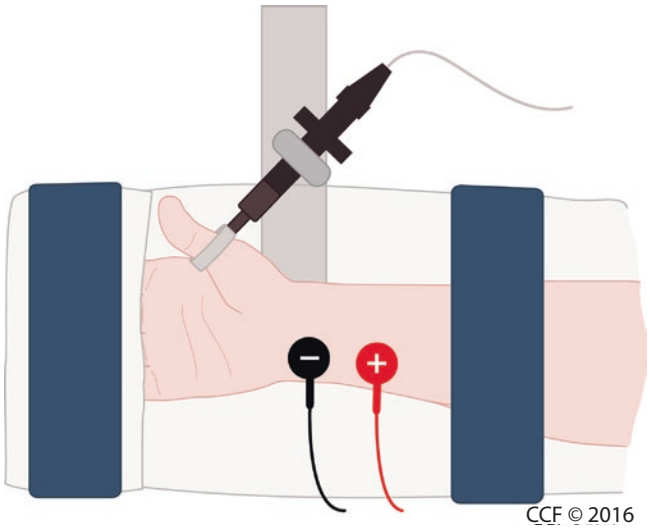

Fig. 8.9 Apparatus for objective monitoring of the adductor pollicis (*thumb*) muscle using mechanomyography. A force transducer ring is attached to the thumb, and the fingers are secured to prevent movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the adductor pollicis muscle, and the force of contraction is measured by the force transducer. The results are displayed on an interfaced screen (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

that have been employed to provide such measurements, and the most clinically relevant techniques will be discussed.

Electromyography (EMG) is the oldest form of neuromuscular monitoring; it measures the electrical potential generated by myocytes upon activation (Fig. 8.8). Active (recording) electrodes are placed over the muscle body (either intramuscular or at the surface), while a neutral electrode is placed at a remote site, usually near the muscle insertion site. EMG signals are subject to electrical interference, direct muscle stimulation, and hypothermia. It should be noted that this modality is inherently different from other techniques in that there is no muscle movement being analyzed; rather, EMG electrodes measure electrical activity (muscle action potential, MAP) in the muscle as a result of pre-synaptic nerve depolarization. EMG measures neuromuscular transmission, and is therefore the most accurate technique of measuring neuromuscular transmission. EMG also has a significant clinical advantage because it does not require the unimpeded movement of the monitored muscle (thumb) that is needed for acceleromyography and kinemyography (see below). Therefore, the monitored arm can be tucked under surgical drapes without affecting EMG recordings.

Mechanomyography (MMG) measures the force created by muscle contraction in response to electrical stimuli applied to peripheral nerves (Fig. 8.9). It is regarded as the gold standard of neuromuscular blockade monitoring, and a mechanomyographic adductor pollicis muscle (APM) TOF ratio of 0.9 or more is widely accepted as the threshold for exclusion of residual paralysis. However, its use in clinical settings is limited by the labor-intensive setup that includes the need for a large rigid support for the arm as well as pre-relaxant calibration and maintenance of a constant 200–300 gm preload (tension). MMG is primarily used for research purposes, as investigators compare new monitoring techniques to MMG.

Acceleromyography (AMG) is based on Newton's second law (force = mass X acceleration) and utilizes a piezoelectric transducer attached to a muscle (Fig. 8.10). Upon stimulation of the nerve and contraction of the muscle, the force of the contraction is determined by measuring the acceleration of the piezoelectric crystal. As this technique relies on the free movement of the thumb and requires access to the hand for monitoring, surgical positioning may limit its clinical use. Nonetheless, multiple large-scale trials have demonstrated that the use of this quantitative monitor will decrease the incidence of postoperative paralysis as compared with the use of subjective assessment.

Kinemyographic (KMG) devices are based on the quantification of the degree of bending of a piezoelectric ceramic-wafer film sensor induced by muscle (thumb) contraction (Fig. 8.11). When the sensor is bent and exposed to motion, it generates an electrical signal that is proportional to the magnitude of bending; the results are then analyzed. Commercially available devices are versatile and mobile, and can be integrated into anesthesia workstations. However, the resulting measurements have been shown not to correlate with the MMG gold standard, limiting its clinical application.

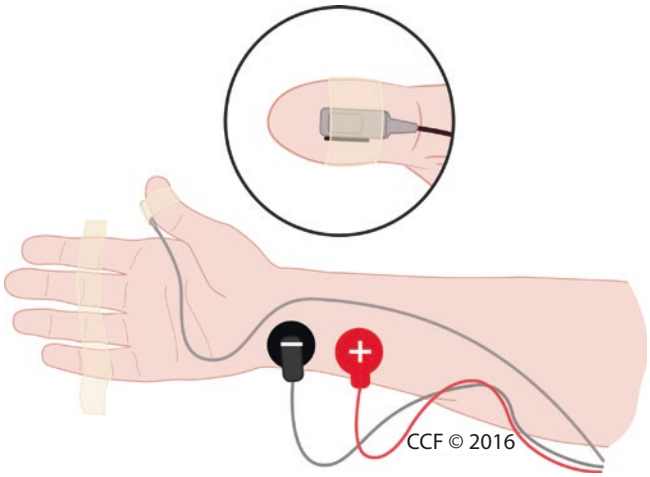

Fig. 8.10 Apparatus for objective monitoring of the adductor pollicis (*thumb*) muscle contraction using acceleromyography. An accelerometer is attached to the thumb and the fingers are secured to prevent movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the adductor pollicis muscle, and the thumb acceleration is measured. The results are displayed on the monitor's screen (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

Fig. 8.11 Apparatus for objective monitoring of the adductor pollicis (*thumb*) muscle contraction using kinemyography. A mechanosensor (*metallic strip*) is placed in the groove between the thumb and index finger; ulnar nerve stimulation produces adductor pollicis muscle contraction that bends the strip, generating a current, which is proportional to the strength of muscle contraction. The results are displayed on the monitor's screen (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

8.8.4 Clinical Considerations

The blockade produced by depolarizing and nondepolarizing NMBDs are distinct and can be distinguished by their response to peripheral nerve stimulation. Succinylcholine-induced (depolarizing) block is characterized by the absence of both fade (to train-of-four or tetanic stimulation) and post-tetanic potentiation in response to nerve stimulation. The block produced by nondepolarizing NMBDs is characterized by fade after repeated stimulation as well as the ability to cause post-tetanic potentiation in which a 5-s tetanic stimulation produces an amplified subsequent response to stimulation. This tetanic stimulus mobilizes pre-junctional calcium, allows for the positive feedback on pre-synaptic acetylcholine receptors, and previously unavailable acetylcholine is released into the synaptic cleft, producing a transiently exaggerated response. It should be noted that succinylcholine can produce fade or post-tetanic potentiation when used in large doses (>10 × ED_{95}), after prolonged exposure (>30 min), or in patients with butyrylcholinesterase deficiency (Fig. 8.12).

Different muscle groups respond differently to the neuromuscular blocking effects of NMBDs. Vessel-rich, large, central muscle groups, such as the diaphragm, are more susceptible to NMBD effects than peripheral muscle groups. Thus, these central muscles become paralyzed before peripheral muscles following administration of NMBDs, and they recover faster. Understanding this relationship is essential to monitoring the level of neuromuscular blockade, regardless of which muscles are being monitored. Whether subjective or objective techniques are being used, monitoring the adductor pollicis muscle in response to ulnar nerve stimulation has been advocated to exclude residual weakness, because the adductor pollicis is one of the last muscles to recover from NMBD-induced paralysis.

Compared to peripheral muscles, the laryngeal and diaphragmatic muscles are more resistant to the effects of neuromuscular blocking drugs (Fig. 8.13). Neuromuscular blockade develops faster, lasts a shorter time, and recovers faster at the laryngeal and diaphragm muscles compared to the adductor pollicis muscle. The diaphragm and larynx have greater total blood flow than the adductor pollicis muscle, resulting in faster delivery of NMBA to these muscles. Conversely, washout of NMBD also occurs faster at the central muscles, so recovery occurs here before it does peripherally. Stimulation of the facial nerve will evoke contraction of the orbicularis oculi muscle (the eyelid) as well as the corrugator supercilii muscle (the eyebrow). The corrugator supercilii muscles have the same time course of paralysis and recovery as the laryngeal adductor muscles, while the orbicularis oculi muscles time course follows peripheral muscles such as the adductor pollicis. Monitoring of facial muscles is a poor substitute for monitoring the adductor pollicis muscle. A recent report showed a 52% incidence of residual paralysis in the recovery room using subjectively assessed eyebrow responses, compared with 22% incidence of residual paralysis during hand muscle monitoring.

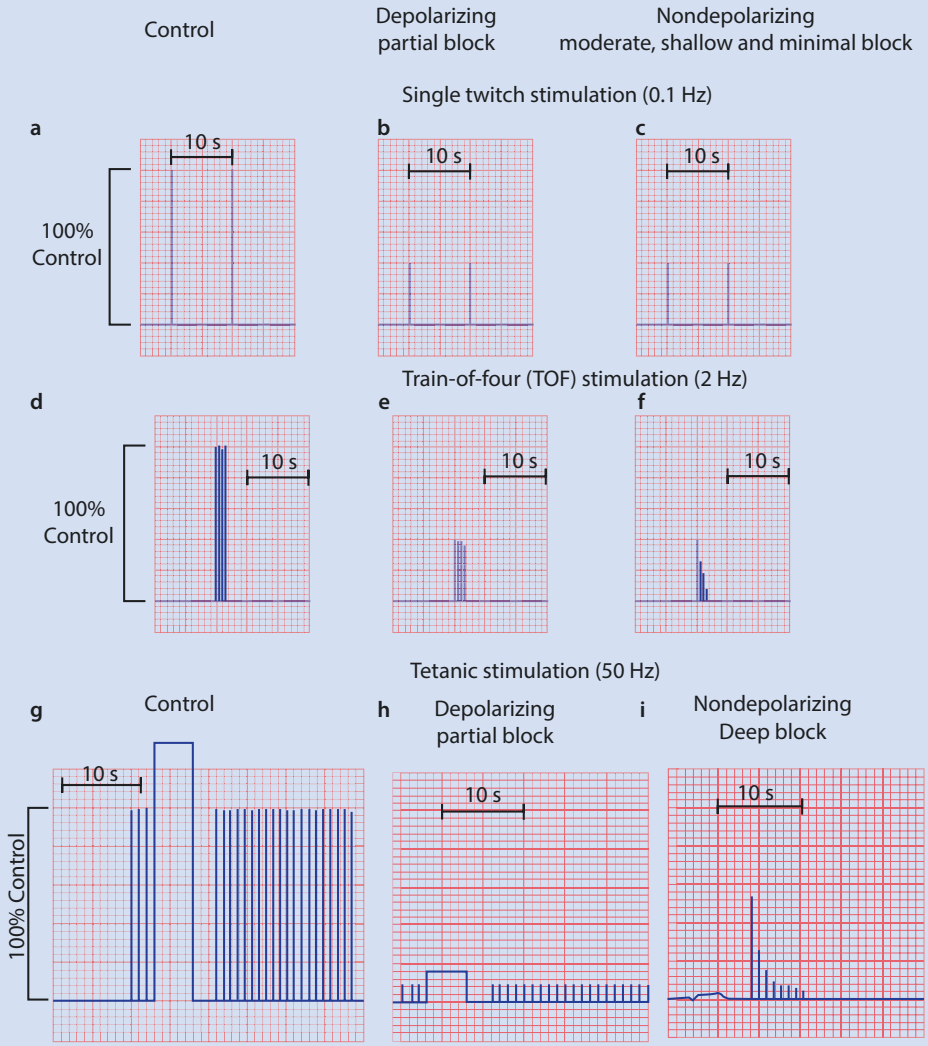

Fig. 8.12 Depiction of muscle contractions in response to single twitch (ST) stimuli delivered at a frequency of 0.1 Hz during normal conduction (Control, **a**); partial depolarizing block **b**; and moderate, shallow or minimal nondepolarizing block **c**. Note the lack of fade between the first ST and subsequent ST evoked responses during both depolarizing and nondepolarizing block when stimuli are delivered at this slow, 0.1 Hz frequency. **Train-of-four (TOF) stimulation.** Train-of-four (*TOF*) pattern in the absence of neuromuscular block (**d**, Control). The TOF ratio (TOFR) is calculated as the ratio between the fourth twitch of the TOF sequence (*T4*) and the first (*T1*). In the unblocked muscle, the TOF ratio is 1.0. During a partial depolarizing block **e**, there is minimal, if any, fade such that the TOF ratio remains close to 1.0. TOF fade is noted during moderate, shallow or minimal nondepolarizing block **f**. **Tetanic stimulation and posttetanic count (PTC). g** In the unblocked muscle, the mechanical response to a 50 Hz tetanic stimulation is characterized by a sustained contraction with virtually no fade in tetanic response or posttetanic potentiation of twitch response. During partial depolarizing block **h**, there is a reduction in the amplitude of tetanic stimulation but there is no tetanic fade or post-tetanic potentiation **i**. Application of tetanus during deep block resulted in a faint contraction for 5 s, and post-tetanic potentiation that results in 8 progressively weaker contractions (PTC = 8). Note that when measuring the PTC one always uses 1 Hz stimulation (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2016. All Rights Reserved)

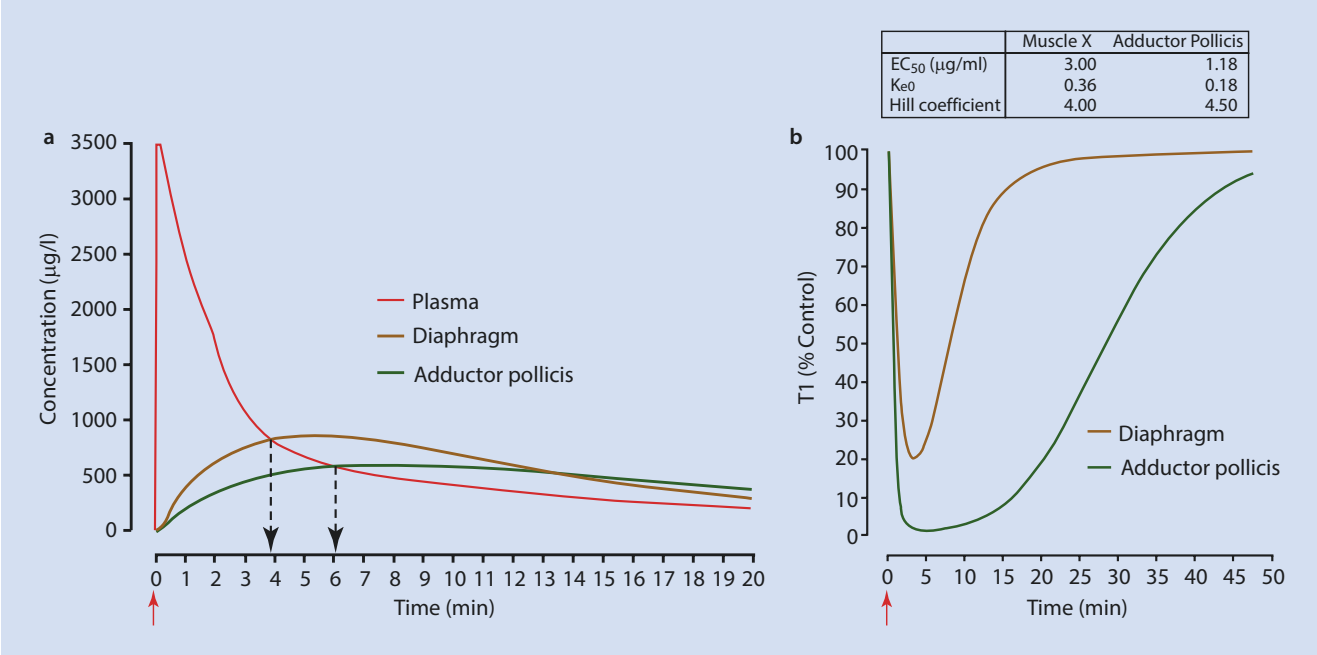

Fig. 8.13 Recovery characteristics of different muscles. Neuromuscular blockade develops faster, lasts a shorter time, and recovers faster at the laryngeal and diaphragmatic muscles than the adductor pollicis muscle although the laryngeal and diaphragmatic muscles are more resistant to neuromuscular blocking drugs. This figure depicts a computer simulation based on published models. Concentrations (*panel A*) and effect (*panel B*) over time for a 0.45 mg/kg rocuronium intravenous bolus. The ED_{95} of rocuronium at the adductor pollicis from this model is 0.33 mg/kg. Rocuronium 0.45 mg/kg is given as a bolus at time zero. Muscle X represents a muscle (such as the diaphragm, the laryngeal adductors, or corrugator supercilii muscle), which is less sensitive to the effects of nondepolarizing relaxants than the adductor pollicis muscle but has greater blood flow. *Panel A* presents the predicted rocuronium plasma and effect site concentrations at the adductor pollicis muscle and muscle X. Note that that concentration of rocuronium reaches higher levels at a faster rate in muscle X than in the adductor pollicis muscle. *Panel B* presents the predicted T1% as a percentage of control at muscle X and the adductor pollicis muscle. The EC_{50} represents the effect site concentration at which there is a 50% probability of effect. The k_{e0} represents the micro rate constant for drug leaving the effect site compartment. The Hill coefficient represents the slope of the effect site concentration versus effect curve (not shown). In this example, the concentration of rocuronium producing 50% block (EC_{50}) of muscle X is 2.5 times that of the adductor pollicis muscle, but the half-life of transport between the plasma and effect compartment ($t_{½}k_{e0}$) of muscle X is only half as long. The rapid equilibration between plasma concentrations of rocuronium and muscle X results in the more rapid onset of blockade at muscle X than at the adductor pollicis muscle. The greater EC_{50} at muscle X explains the faster recovery of this muscle from neuromuscular block (faster rocuronium wash-out) than at the adductor pollicis muscle (Reproduced with permission from Naguib and Kopman [22])

8.9 Questions and Answers

Questions (Choose the most Appropriate Answer)

1. Atracurium is metabolized through mechanisms that are similar to all of the following **except**:
   - A. Esmolol
   - B. Chloroprocaine
   - C. Remifentanil
   - D. Oseltamivir
   - E. Cisatracurium
2. Following a rapid sequence dose of rocuronium for a 100-kg patient, if you decide to reverse the block with sugammadex after 5 min, which of the following doses is appropriate:
   - A. 100 mg
   - B. 200 mg
   - C. 400 mg
   - D. 1600 mg
   - E. 2000 mg
3. Which of the following clinical conditions can cause a prolonged response to nondepolarizing neuromuscular blockade:
   - A. Propofol as the primary anesthetic
   - B. Patient receiving chronic calcium channel blocker treatment for hypertension
   - C. Patients with a contraction alkalosis from diuretic use
   - D. A pregnant patient with eclamptic seizures being treated with intravenous magnesium
   - E. All of the above can prolong the response to nondepolarizing neuromuscular blockade
4. Full recovery from neuromuscular blockade is defined as:
   - A. A sustained 5-s head lift
   - B. Presence of all 4 twitches elicited from a peripheral nerve stimulator with electrodes along the facial nerve
   - C. Tidal volumes greater than 8 cc/kg on a spontaneous ventilation mode in an intubated patient

D. A train-of-four (TOF) ratio greater than or equal to 0.9 as determined by a quantitative monitoring device of the adductor pollicis muscle
E. All of the above represent definitive means of establishing complete reversal and recovery from neuromuscular blockade

5. Neostigmine-induced reversal of neuromuscular blockade can be delayed by which of the following conditions:
A. Presence of a deep level of neuromuscular block
B. Vecuronium block in elderly patients
C. Patients whose primary anesthetic was sevoflurane
D. Patients who received pancuronium
E. All of the factors can prolong neostigmine reversal
6. Following a bolus dose of rocuronium, the order of muscle groups that will become paralyzed is:
A. Diaphragm → orbicularis oculi
B. Corrugator supercilii → laryngeal adductors
C. Adductor pollicis → laryngeal adductors
D. Flexor hallucis brevis → diaphragm
E. Orbicularis oculi → corrugator supercilii
7. Upregulation of extrajunctional nicotinic receptors occurs in all of the following states **except:**
A. After burns that cover more than 50% of total body surface area
B. Within the first hours following a cervical neck fracture severing the spinal cord
C. A septic shock patient who has been intubated, sedated, and receiving mechanical ventilation for 3 weeks
D. An ICU patient with severe acute respiratory distress syndrome (ARDS) receiving a cisatracurium infusion for the past week
E. A patient who experienced a stroke and subsequent hemiplegia several years ago
8. Succinylcholine administration is associated with:
A. Rare instances of postoperative myalgias (<5%)
B. Increasing intragastric pressure that significantly increases the risk of aspiration
C. A transient decrease in intraocular pressure
D. An exaggerated hyperkalemic response in patients with end stage renal disease
E. The potential for triggering malignant hyperthermia
9. Mivacurium is metabolized through a mechanism similar to:
A. Atracurium
B. Succinylcholine
C. Pancuronium
D. Rocuronium
E. Vecuronium
10. Sugammadex reversal is associated with which of the following:
A. Rapid reversal of neuromuscular blockade from cisatracurium administration
B. A clinically relevant increase in bleeding
C. A cessation of the need to utilize quantitative monitors to determine the depth of neuromuscular blockade
D. A disruption in the effectiveness of oral contraceptives
E. Rapid reversal of succinylcholine-induced neuromuscular blockade

Answers

1. **B.** In addition to the Hofman reaction, atracurium is metabolized by non-specific plasma esterases, as is esmolol, remifentanil, and oseltamivir. Chloroprocaine is metabolized by butyrylcholinesterase.
2. **D.** The dose of sugammadex to reverse profound levels of neuromuscular blockade immediately after a rapid sequence dose of rocuronium is 16 mg/kg. This translates to a dose of 1600 mg in a 100 kg patient. Deep neuromuscular blockade with 1–2 post-tetanic twitches present can be reversed with a sugammadex dose of 4 mg/kg. Lighter levels of blockade, with at least 2 of 4 twitches present after a train-of-four stimulation can be reversed with sugammadex at a dose of 2 mg/kg.
3. **D.** The parturient receiving a magnesium infusion may have hypermagnesemia, a condition that prolongs the normal response to neuromuscular blockade by preventing the release of acetylcholine from the presynaptic junction. Inhalational anesthetics, rather than intravenous agents such as propofol, can also prolong neuromuscular blockade. While hypocalcemia prolongs neuromuscular blockade by similar mechanisms as hypercalcemia, patients on chronic calcium channel blockers do not have a clinically significant prolonged response to neuromuscular blockade. Acidosis, rather than alkalosis, also prolongs the response to neuromuscular blocking drugs.
4. **D.** The gold standard for determining recovery from neuromuscular blockade is a train-of-four ratio ≥0.9 as determined by monitoring the adductor pollicis muscle response via mechanomyography. Clinical tests such as assessing tidal volumes, negative inspiratory force, and sustained head lift do not reliably exclude residual paralysis. Furthermore, 4 of 4 twitches observed after train-of-four stimulation of the facial nerve can still be present despite up to ~30% of nicotinic receptors being blocked and such a response does not exclude residual paralysis.
5. **E.** Reversal with neostigmine is dependent on a number of variables and should not occur when patients have deep levels of neuromuscular blockade (eg, when only post-tetanic twitches are present). The response can be prolonged in the

elderly, in patients who received inhalational anesthetics, and following administration of long-acting NMBAs such as pancuronium.

6. **A**. Central muscles receive a higher proportion of blood flow and are more susceptible to the relaxant effects of NMBA than peripheral muscles. After administration of NMBA, the central muscles, such as the diaphragm and laryngeal adductors, are affected first. These muscles are also the first to recover. The response of corrugator supercilli muscle is similar to that of the laryngeal adductors while the orbicularis oculi mirrors the adductor pollicis muscle response.
7. **B**. Upregulation of extrajunctional nicotinic receptors occurs in a variety of settings, such as following major burns, in the intensive care unit after chronic debility from illnesses such as sepsis, after long term NMB infusion, and in patients with history of stroke with resultant weakness. In the case of acute paralysis from recent (within hours) spinal cord transection, upregulation has not occurred yet.
8. **E**. The incidence of postoperative myalgias from succinylcholine is high (~50%). While administration of this agent is associated with increased intragastric pressure, the lower esophageal sphincter tone also increases, negating any potential increase in risk of aspiration. In fact, succinylcholine is commonly the drug of choice when aspiration is a concern given its reliably fast onset. While succinylcholine increases plasma potassium levels (~0.5 mEq), an exaggerated response is not noted in patients with end stage renal disease. These patients commonly have preoperative hyperkalemia, but potassium levels increase similarly to that of the general population. Succinylcholine is a potent trigger for malignant hyperthermia, particularly when combined with inhalational anesthetics.
9. **B**. Mivacurium is metabolized through butyrylcholinesterase, just as succinylcholine (and chloroprocaine). Atracurium undergoes Hofman reaction degradation and metabolism through plasma esterases. Pancuronium, rocuronium, and vecuronium are eliminated via the liver and kidney.
10. **D**. Sugammadex cannot reverse neuromuscular blockade from cisatracurium. It has been reported that within the first 60 min of sugammadex reversal, prothrombin time increases by 3% and activated partial thromboplastin time increases by 5.5%, but no increase in bleeding has been reported with use of sugammadex. The dose of sugammadex depends on the level of neuromuscular blockade and thus the need for quantitative monitoring to determine such. It does not reverse succinylcholine. Sugammadex binds oral contraceptives and is equivalent to missing 1 dose of such medications. Patients on these agents should be advised to utilize alternative forms of birth control up to 2 weeks afterwards.

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