Chapter 7: Muscle Relaxants

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INTRODUCTION

FOCUS POINTS

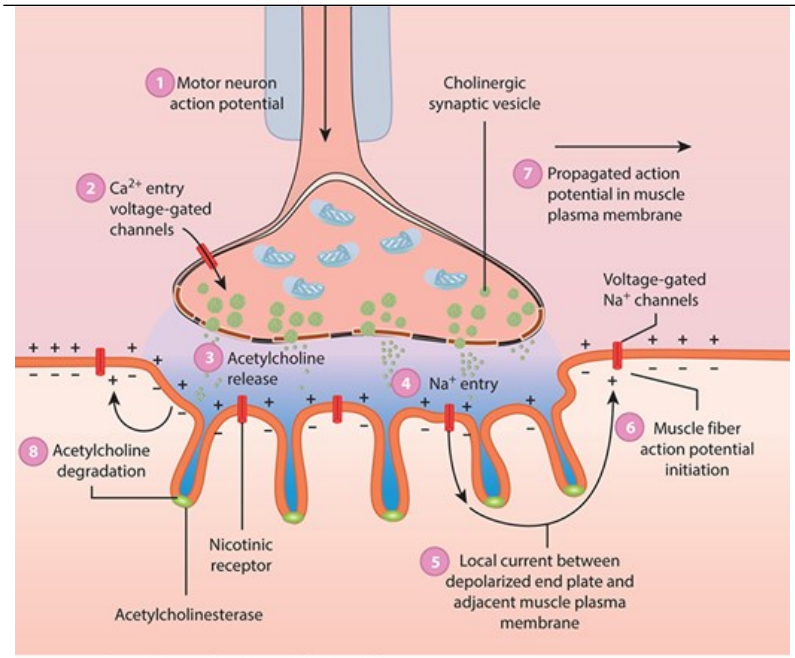
1. Neuromuscular blocking drugs (NMBDs) are quaternary ammonium compounds that have structural similarities to acetylcholine (Ach).
2. The *potency* of a NMBD is a measure of the dose required to produce the corresponding twitch suppression.
3. The *onset time* is the time from administration to maximum blockade.
4. The *duration of action* is the time to return to 25% of baseline single twitch height (T25).
5. Succinylcholine is the only clinically available depolarizing NMBD and is hydrolyzed by plasma cholinesterase (also referred to as butyrylcholinesterase or pseudocholinesterase).
6. The efficacy of a patient's plasma cholinesterase can be expressed by the dibucaine number.
7. Contraindications to succinylcholine administration include personal or family history of malignant hyperthermia, known or suspected myopathy, hyperkalemia, and medical conditions that result in increased extrajunctional acetylcholine receptors such as burns, trauma, and immobility.
8. The routine use of succinylcholine in infants and children should be avoided due to the risk of hyperkalemic cardiac arrest in patients with undiagnosed skeletal muscle myopathy.
9. There are two chemical classes of clinically available nondepolarizing NMBDs: the aminosteroid compounds (pancuronium, vecuronium, rocuronium) and the benzylisoquinolinium compounds (atracurium, cisatracurium, mivacurium).
10. There are two classes of agents for reversal of neuromuscular blockade: anticholinesterases and cyclodextrins.

PHYSIOLOGY OF THE NEUROMUSCULAR JUNCTION

The neuromuscular junction consists of the prejunctional motor neuron, synaptic cleft, and postsynaptic endplate of the skeletal muscle membrane (Figure 7-1).[1] Neuromuscular transmission begins when an action potential in the prejunctional motor neuron reaches the nerve terminal. The arrival of the action potential triggers the opening of voltage-gated calcium channels, leading to the influx of calcium ions. The increase in calcium results in fusion of vesicles containing acetylcholine (ACh) molecules with the membrane of the nerve terminal, thus releasing ACh into the synaptic cleft by exocytosis. ACh serves as the neurotransmitter at the neuromuscular junction and is synthesized and stored in vesicles at the motor nerve terminal.[2]

Figure 7-1

The neuromuscular junction. (Adapted with permission, from Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology: The Mechanisms of Body Function*. 11th ed. 2008. Copyright © McGraw Hill LLC. All rights reserved.)



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ACh released into the synaptic cleft diffuses to the motor endplate and binds to nicotinic ACh receptors. The ACh receptor consists of five subunits arranged in a rosette to form an ion channel. The simultaneous binding of two ACh molecules to the two α subunits of the ACh receptor causes the channel to open, allowing inward movement of sodium ions and outward movement of potassium ions. The increase in intracellular sodium depolarizes the membrane, generating an action potential that propagates along the length of the muscle fiber, leading to muscular contraction. Once in the synaptic cleft, ACh is rapidly hydrolyzed by acetylcholinesterase. The motor nerve ending also reuptakes ACh.[3]

ACh receptors are located at prejunctional, postjunctional, and extrajunctional locations and have different composition of subunits. The prejunctional ACh receptors are composed of two α3 and three β2 subunits and are thought to modulate ACh release via a positive feedback system to mobilize ACh vesicles. The adult postjunctional ACh receptor is composed of two α1, one β1, one δ, and one ε subunit (α2βδε) (Figure 7-2).[4,5] In the fetal ACh receptor, the ε subunit is replaced by a γ subunit (α2βδγ) (Figure 7-3).[6] During early development, fetal ACh receptors are present throughout the length of the muscle fiber. Late in fetal development, the γ subunit is replaced by the ε subunit, such that at term a neonate has both adult and fetal ACh receptors, with a predominance of adult ACh receptors.[7] Extrajunctional ACh receptors are located outside of the neuromuscular junction and have the same structure as fetal ACh receptors. Synthesis of extrajunctional receptors is suppressed under normal conditions.

Figure 7-2

The adult acetylcholine receptor composed of two α, one β, one δ, and one ε subunits (α2βδε) arranged in a rosette. (Reproduced with permission, from Mashour GA, Lydic R, eds. *The Neuroscientific Foundations of Anesthesiology*. 2011. Copyright © Oxford University Press. All rights reserved.)

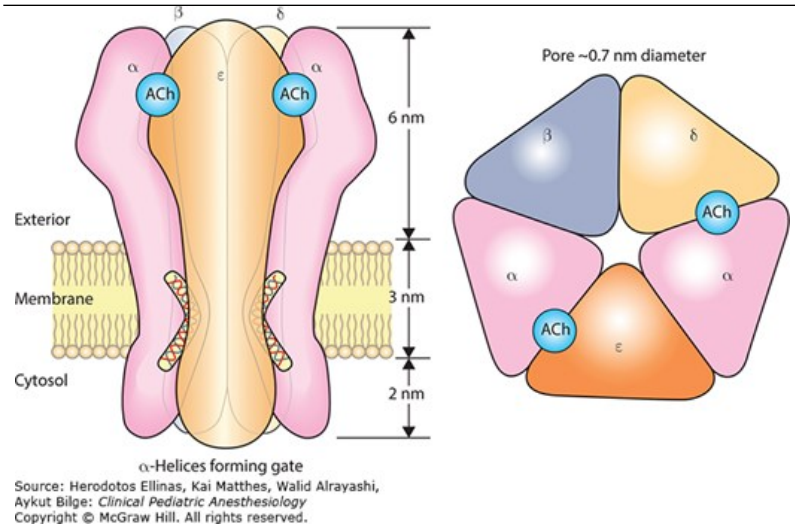
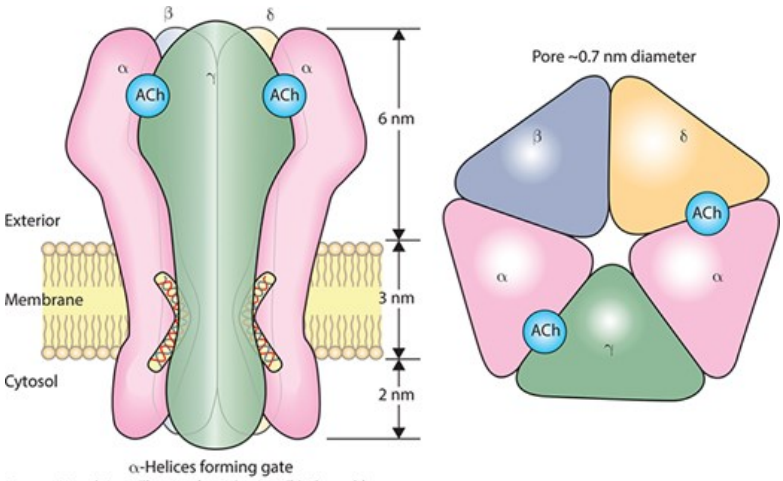


Figure 7-3

The fetal acetylcholine receptor is similar in structure to the adult acetylcholine receptor, except the ε subunit is replaced by a γ subunit (α2βδγ). Extrajunctional acetylcholine receptors have the same composition. (Reproduced with permission, from Mashour GA, Lydic R, eds. *The Neuroscientific Foundations of Anesthesiology*. 2011. Copyright © Oxford University Press. All rights reserved.)



NEUROMUSCULAR TRANSMISSION IN THE NEONATE

Neuromuscular transmission in the neonate differs from older children and adults. At birth, infants have both fetal and adult ACh receptors. The adult subtype replaces the fetal subtype during the first 2 to 4 years of life. Compared to the adult subtype, the fetal ACh receptor is a low-conductance channel. The fetal subtype has a slower response to ACh and has a prolonged open channel time once it is depolarized.[8] The fetal receptor is more sensitive to succinylcholine and more resistant to nondepolarizing neuromuscular blockers compared to the adult subtype. Neonates younger than 2 months deplete acetylcholine reserves faster than older infants in response to tetanic nerve stimulation.[9,10]

NEUROMUSCULAR MONITORING

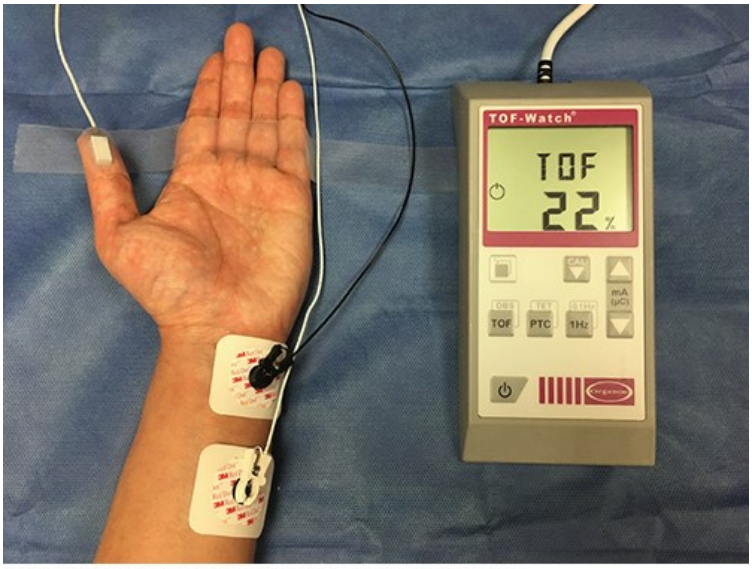
Neuromuscular junction function is assessed by visual, tactile, or recording of the response of a peripheral nerve to electrical stimulation. Neuromuscular monitoring assesses the depth and recovery of blockade after administration of a NMBD. Superficial electrodes are placed over a

peripheral nerve and various patterns of supramaximal electrical stimulation are applied. Commonly, the adductor pollicis muscle of the thumb is monitored by stimulation of the ulnar nerve. Other muscles such as the orbicularis oculi muscle of the face and the flexor hallucis muscle of the foot can also be monitored. NMBDs have different effects on various muscle groups with respect to time of onset, depth, and duration of action. For example, the dose of pancuronium in infants and children for blockade of the diaphragm is higher than for the adductor pollicis.[11] Recovery of the central muscles is also faster than for peripheral muscles. In this regard, recovery of peripheral neuromuscular function suggests that the vocal cords and diaphragm are at a more advanced state of recovery.

Assessment of the response to a stimulus can be qualitative or quantitative. The easiest and least expensive method is qualitative with visual or tactile evaluation. However, even experienced anesthesiologists may be unable to detect fade using subjective evaluation of train-of-four stimulation.[12] Various methods can be used for objective monitoring. Commercially available monitors for quantitative measurement are based on the acceleration of the muscle response (acceleromyography) (Figure 7-4), the electrical response of the muscle (electromyography), and the evoked electrical response from a piezoelectric sensor attached to the muscle (kinemyography).[13]

Figure 7-4

Nerve monitoring based on acceleromyography provides a quantitative assessment of neuromuscular blockade. The display shows the train of four ratio as a percentage. (Photo courtesy of Dr. Albert C. Yeung.)



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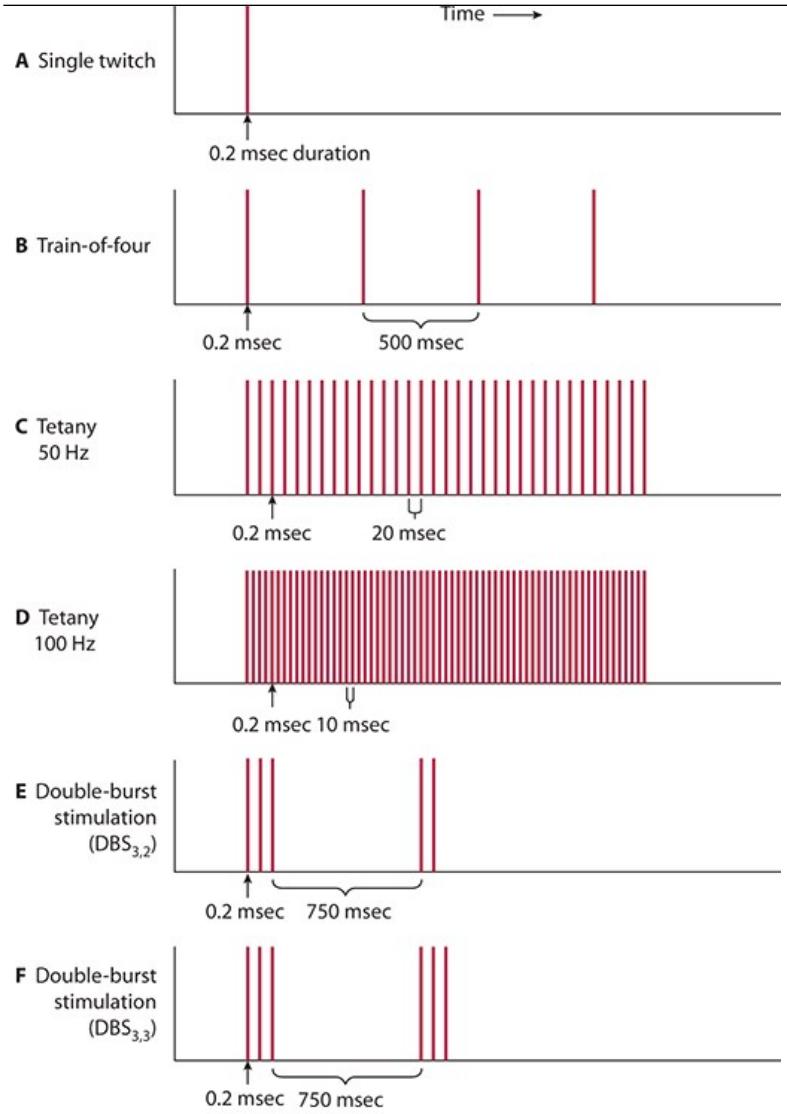
PATTERNS OF STIMULI

Modes of stimulation in clinical practice include single twitch, train-of-four ratio, tetanic stimulation, post-tetanic stimulation, and double burst suppression (Figure 7-5).[14] In single twitch, a single stimulus at intervals greater than 10 seconds is applied to a nerve. The amplitude response after administration of a NMBD is compared to the baseline twitch before neuromuscular blockade. The depth of blockade is expressed as the percentage block from baseline. Clinical use of single twitch monitoring is limited because a control value is required.

Figure 7-5

Modes of stimulation for monitoring of neuromuscular blockade. (Reproduced with permission, from Butterworth IV JF, Mackey DC, Wasnick JD. eds. *Morgan & Mikhail's Clinical Anesthesiology*, 6th ed. 2013. http://accessanesthesiology.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



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Train-of-four (TOF) stimulation is the most commonly used pattern of monitoring for nondepolarizing neuromuscular blockade. Unlike single twitch, no baseline measurement is required. TOF stimulation consists of four supramaximal stimuli given every 0.5 seconds. Each successive stimulus depletes ACh, resulting in a "fade" in the setting of partial neuromuscular blockade. The TOF ratio is the amplitude of the fourth twitch compared to the first twitch. Prior to administration of a NMBD, the TOF ratio should be 1.0. Full-term infants under 1 month of age and premature infants have a reduced ratio, likely reflective of the immature neuromuscular junction. By the age of 2 months, the TOF ratio is near 1.0.[15] In clinical practice, a TOF ratio of >0.9 indicates adequate recovery from neuromuscular blockade.[16]

With TOF monitoring, the depolarizing block from succinylcholine initially produces what is referred to as a phase 1 block. As twitches return after a single dose of succinylcholine, all four twitches are decreased by a similar amount such that there is no fade and the TOF ratio remains near 1.0 (Figure 7-6).[17] With increasing doses of succinylcholine, such as with a large single dose or repeated doses, a phase 2 block can develop. A phase 2 block shows fade with TOF stimulation like a nondepolarizing blockade.[18]

Figure 7-6

Train-of-four monitoring after administration of nondepolarizing and depolarizing NMBDs. (Reproduced with permission, from Freeman BS, Berger JS. eds. *Anesthesiology Core Review: Part One Basic Exam*. 2014. http://accessanesthesiology.mhmedical.com. Copyright © McGraw Hill LLC. All rights

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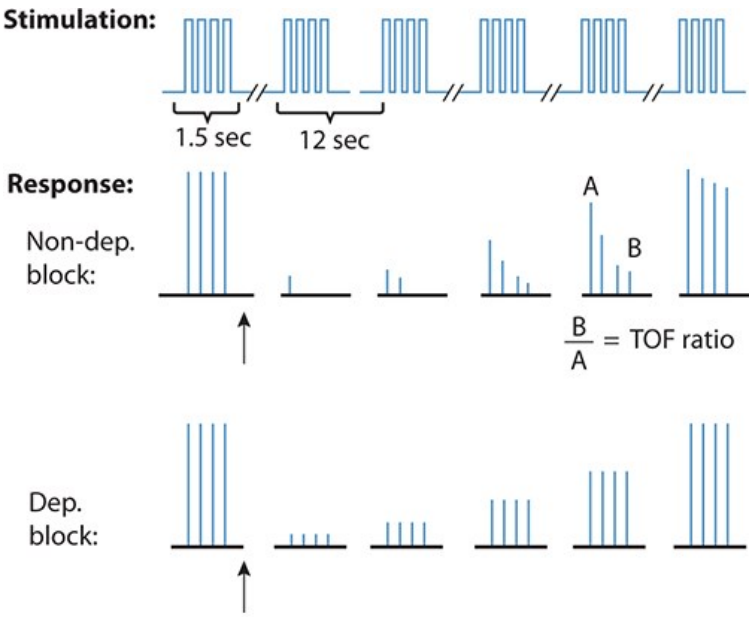

Source: Herodotos Ellinas, Kai Matthes, Walid Alrayashi, Aykut Bilge: *Clinical Pediatric Anesthesiology*

Tetanus is the rapid delivery of electrical stimulus, most commonly for 5 seconds at 50 hertz (Hz). At baseline, such a stimulus does not result in fade. In the presence of nondepolarizing neuromuscular blockade, tetanic fade is present. Tetanic stimulation can be used to detect residual neuromuscular blockade but is painful in an unanesthetized patient. Tetanic stimulation increases quantities of ACh in the neuromuscular junction, producing post-tetanic facilitation with a brief period of increased twitch tension after tetanic stimulation.[19]

Post-tetanic count (PTC) stimulation can be used to monitor the degree of neuromuscular blockade after a large dose of a nondepolarizing NMBD. With profound blockade, there is no contractile response to single twitch or TOF stimulus. PTC is based on the principle of post-tetanic facilitation. To assess PTC, a tetanic stimulus is followed by a 3-second pause and then a series of single-twitch stimuli at 1 Hz. As the profound block dissipates, post-tetanic twitches will be visible. In children who have received 1 mg/kg of rocuronium, the presence of one PTC twitch predicts the return of response to TOF stimulation in 7 minutes.[20]

Double-burst stimulation (DBS) is two short tetanic stimulations at 50-Hz separated by 750 milliseconds. The ratio of the second to the first stimulus is assessed for fade. DBS was developed as a method to manually detect fade that cannot be perceived in TOF monitoring. The ability of the anesthesiologist to manually detect fade in both children and adults is greater with DBS than with TOF monitoring.[21] However, the absence of fade with DBS is not an indicator that the TOF ratio is >0.9.

MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING DRUGS

NMBDs are quaternary ammonium compounds that have structural similarities to ACh. The drugs can be classified as depolarizing or nondepolarizing NMBDs. Succinylcholine is the only depolarizing NMBD in clinical use. It is composed of two ACh molecules linked together by their methyl groups and mimics ACh by binding to the ACh receptor, resulting in opening of the ion channel. Depolarization of the postjunctional membrane generates muscle contraction (fasciculations), followed by a period of relaxation as the motor end plate remains depolarized. Unlike ACh, succinylcholine is not hydrolyzed by acetylcholinesterase at the neuromuscular junction and is instead eliminated in the plasma by plasma cholinesterase (also referred to as butyrylcholinesterase or pseudocholinesterase).[22]

Nondepolarizing NMBDs impair neuromuscular transmission primarily as competitive antagonists of ACh by blocking the binding of endogenous ACh to its postjunctional receptor.[23] They competitively bind the α subunit of postjunctional ACh receptors, preventing depolarization. No fasciculations occur with the onset of blockade.[24]

PHARMACOLOGIC PROPERTIES OF NEUROMUSCULAR BLOCKING DRUGS

The *potency* of a NMBD is a measure of the dose required to produce the corresponding twitch suppression. The effective dose 95 (ED95) of a NMBD is the dose that produces a 95% depression of the single twitch height. In general, a dose of two to three times the ED95 is suggested to achieve intubating conditions. Recommended maintenance doses are ¼ to ⅓ of the intubating dose. The *onset time* is the time from administration to maximum blockade. Potent drugs have a slower onset time compared to less potent ones. The *duration of action* is the time to return to 25% of baseline single twitch height (T25). Medications that have rapid plasma clearance have a shorter duration of action compared to agents that are slowly eliminated from the plasma. The *recovery index* is the duration between 25% and 75% recovery of twitch height.[25,26]

Infants and children exhibit some differences compared to adults in their pharmacologic responses to NMBDs. The factors contributing to the variations may be due to age-related differences in the maturity of the neuromuscular junction, the volume of distribution, and clearance. In particular, infants are more sensitive to NMBDs compared to children and adults.[27] The onset time tends to be faster in infants compared to older children and adults, but the duration of action and recovery index are longer in infants compared to children.[28] The ED95 value tends to be higher in children than in infants and adults.[29]

DEPOLARIZING NEUROMUSCULAR BLOCKING DRUG: SUCCINYLCHOLINE

Succinylcholine is the only clinically available depolarizing NMBD. It binds the ACh receptor at the neuromuscular junction, resulting in depolarization of the postjunctional membrane. Succinylcholine has a rapid onset time and a short duration of action in most individuals, which makes it an ideal drug for a rapid-sequence induction for intubation. Depolarization of the postjunctional membrane manifests as general skeletal muscle contractions known as fasciculations, followed by relaxation.

Pharmacology of Succinylcholine

The dose requirement for succinylcholine is higher in infants and children compared to adults. The ED90 in neonates and infants are 517 and 608 mcg/kg, respectively, compared to 290 mcg/kg in adults. The higher ED90 may be reflective of the higher volume of distribution in infants and children. The suggested intubating dose is 3 mg/kg for infants and 1.5 to 2 mg/kg for children, compared to 1 mg/kg in adults.[30] Succinylcholine can also be administered intramuscularly. For children, 3 to 4 mg/kg of intramuscular succinylcholine will provide relaxation for intubation.[31] For treatment of laryngospasm, a much lower dose (such as 0.1 mg/kg) may be sufficient to allow positive pressure ventilation.[32] As succinylcholine both rapidly reaches the neuromuscular junction and becomes hydrolyzed by plasma cholinesterase, the maximum effect is achieved quickly. The elimination half-life is less than 1 minute.

The duration of action for succinylcholine is prolonged in patients with decreased or abnormal plasma cholinesterase. Plasma cholinesterase is synthesized by the liver. Plasma cholinesterase deficiency in the setting of severe disease may lead to moderate increases in the duration of action. Patients with atypical variants of plasma cholinesterase that result in decreased enzyme activity or quantity will experience prolonged blockade after administration of succinylcholine.[33] In patients who are heterozygous with one atypical allele of plasma cholinesterase, the duration of the block from succinylcholine may be lengthened 50% to 100%. A patient who is homozygous for atypical plasma cholinesterase may have blockade for several hours.[34]

The efficacy of a patient's plasma cholinesterase can be expressed by the dibucaine number (Table 7-1). Dibucaine is a local anesthetic that inhibits the activity of normal plasma cholinesterase by about 70% to 80%.[35] The dibucaine number is expressed as the percent inhibition of this enzyme. Thus, a patient with normal enzymatic activity will have a dibucaine number of 70 to 80. Patients heterozygous for atypical plasma cholinesterase will have inhibition of 50% to 60% and those who are homozygous will have inhibition of about 20% to 30%.

Table 7-1

Dibucaine Number and Response to Succinylcholine

Type of Plasma Cholinesterase	Homozygous Typical	Heterozygous	Homozygous Atypical
Dibucaine number (% inhibition)	70–80	50–60	20–30
Duration of blockade	Normal	Lengthened 50–100%	Lengthened 4–8 h

Side Effects of Succinylcholine

While useful for rapid neuromuscular blockade, succinylcholine has multiple adverse side effects that limit its routine use in pediatric anesthesia (Table 7-2).

Table 7-2

Adverse Side Effects of Succinylcholine

Cardiac • Bradyarrhythmia • Junctional rhythm • Ventricular dysrhythmia • Tachycardia
Hyperkalemia
Increased intracranial pressure
Increased intraocular pressure
Myalgia
Myoglobinemia
Trismus
Triggering agent for malignant hyperthermia

Cardiac

Due to its structural relationship to ACh, succinylcholine stimulates cholinergic autonomic receptors. Arrhythmias such as bradycardia, junctional rhythms, tachycardia, and ventricular dysrhythmias can occur from administration of succinylcholine.[36] The bradycardia and junctional rhythms may be due to activation of cardiac postganglionic muscarinic receptors, with succinylcholine mimicking the effects of ACh. Bradyarrhythmias can be more pronounced when a second dose of succinylcholine is given but do not seem to occur after intramuscular injection. Administration of an anticholinergic such as atropine can prevent the bradycardic response to succinylcholine.[37] Succinylcholine can also increase catecholamine levels, resulting in tachycardia and ventricular dysrhythmias.

Hyperkalemia

Binding of succinylcholine to the ACh receptor opens the voltage-gated sodium channel, resulting in the influx of sodium ions and the efflux of potassium ions. Administration of succinylcholine results in an increase of up to 1 mEq/L of plasma potassium in children.[38] Patients with denervation injuries, prolonged immobilization, or burn injuries may have upregulation of extrajunctional acetylcholine receptors, leading to an exaggerated hyperkalemic response to succinylcholine. Life-threatening hyperkalemia after succinylcholine can occur in patients with neuromuscular diseases such as muscular dystrophy, upper and lower motor neuron lesions, burns, trauma, and prolonged immobilization from critical illness.[39]

Hyperkalemic cardiac arrest after succinylcholine has been reported in apparently healthy children who were subsequently diagnosed with muscular dystrophy.[40] This led the United States Food and Drug Administration (FDA) to issue a warning that "the use of succinylcholine in pediatric patients should be reserved for emergency intubation or instances where immediate securing of the airway is necessary, eg, laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible."[41]

Increased Intracranial Pressure and Intraocular Pressure

Succinylcholine can increase intracranial pressure. The increase in intracranial pressure may be attenuated by pretreatment with a nondepolarizing NMBD.[42] Intraocular pressure increases about 1 minute after administration of succinylcholine and returns to baseline in 5 to 10 minutes. The increase in intraocular pressure has led to the recommendation that succinylcholine be avoided in patients with an open-eye injury. However, there is scant evidence that use of succinylcholine leads to extrusion of ocular contents in such patients.[43]

Fasciculations, Myalgia, and Myoglobinemia

Fasciculations can be observed in children and adolescents and less commonly in infants. Pretreatment with a low dose (10–30% of ED95) of a nondepolarizing NMBD can prevent fasciculation and may ameliorate resulting muscle pain.[44] Myoglobinemia can occur but is rarely of clinical significance.[45]

Trismus and Malignant Hyperthermia

Masseter jaw rigidity can occur after succinylcholine administration, particularly with halothane anesthesia. In extreme cases, trismus can be so severe that strong force may be required to open the mouth for intubation. Incomplete jaw relaxation can be seen in up to 4.4% of children receiving succinylcholine during halothane anesthesia.[46] Masseter muscle rigidity can be seen with malignant hyperthermia, but masseter spasm alone is not diagnostic. While some have advocated taking malignant hyperthermia precautions if masseter jaw rigidity develops, others propose that masseter spasm alone is not an indication to switch to a non-triggering anesthetic.[47] Succinylcholine is a trigger for malignant hyperthermia in susceptible patients.

INDICATIONS AND CONTRAINDICATIONS FOR SUCCINYLCHOLINE USE IN INFANTS AND CHILDREN

The rapid onset and short duration of action make succinylcholine an ideal agent for rapid-sequence tracheal intubation and for treatment of laryngospasm. With a dose of 2 mg/kg, twitch suppression of 95% occurs within 36 seconds in infants and children.[48] Due to the potential for bradyarrhythmias, administration of atropine 0.01 to 0.02 mg/kg prior to succinylcholine should be considered especially in children with Trisomy 21. An alternative to succinylcholine for a rapid sequence induction is rocuronium 1.2 mg/kg, which can produce intubating conditions similar to those after succinylcholine in children.[49]

The routine use of succinylcholine in infants and children is not advised due to the risk of cardiac arrest and hyperkalemia in children with undiagnosed Duchenne's muscular dystrophy, particularly in males 8 years of age or younger. The FDA has a "black box" warning stating that succinylcholine use in pediatric patients should be limited to emergency airway control. Contraindications to succinylcholine are personal or family history of malignant hyperthermia, known or suspected myopathy, hyperkalemia, and medical conditions that result in increased extrajunctional acetylcholine receptors such as burns, trauma, and immobility.

NONDEPOLARIZING NEUROMUSCULAR BLOCKADE DRUGS

Nondepolarizing NMBDs compete with endogenous ACh at the neuromuscular junction, preventing postjunctional depolarization required for muscle contraction. There are several nondepolarizing NMBDs available for clinical use. Selection of one drug over another should take into account the onset, duration of action, side effects, metabolism, and clearance of the individual medication.

Nondepolarizing NMBDs can be classified according to onset, duration of action, or chemical class. The onset is inversely related to the potency of the drug (Table 7-4). At equipotent doses the onset time is more rapid in drugs with lower potency.[50] The duration of action can be classified as short-acting (duration 10–20 minutes), intermediate-acting (duration 20–50 minutes), and long-acting (duration >50 minutes) (Table 7-3). There are two chemical classes of clinically available nondepolarizing NMBDs: the aminosteroid compounds (pancuronium, vecuronium, rocuronium) and the benzylisoquinolinium compounds (atracurium, cisatracurium, mivacurium).

Table 7-3

Classification of Nondepolarizing NMBDs

Short-acting (duration 10–20 min) • Mivacurium
Intermediate-acting (duration 20–50 min) • Atracurium • Cisatracurium • Rocuronium • Vecuronium
Long-acting (duration >50 min) • Pancuronium

Table 7-4

Comparison of NMBDs for Intubation

Drug	Intubating Dose (mg/kg)	Onset Time (minutes)
Succinylcholine	3 (infant)	0.5–1
	1.5–2 (children)	
Mivacurium	0.25	1.5–2
Atracurium	0.5	1–1.4
Cisatracurium	0.15	2–3
Rocuronium	0.45 (infant)	1.5
	0.6 (children)	
	1.2 (rapid sequence induction in children)	0.7
Vecuronium	0.1	1–2
Pancuronium	0.1	3

There are various side effects associated with nondepolarizing NMBDs.[51] An increase in heart rate can be seen with administration of pancuronium and rocuronium. A vagolytic effect appears to occur with pancuronium. With rocuronium, it is unclear whether the increase in heart rate is due to pain on injection (pH adjusted with acetic acid and/or sodium hydroxide) or a direct chronotropic effect. Histamine release, with transient flushing and hypotension, is most frequently associated with benzylisoquinolinium drugs. NMBDs are the most common medication class in anesthetic-related hypersensitivity reactions[52] with anaphylaxis being an uncommon but serious complication. Despite sharing structural similarities to steroids, the aminosteroids do not possess hormonal activity.

Nondepolarizing NMBDs have various modes of metabolism (Table 7-5). The benzylisoquinolinium compounds undergo organ-independent degradation. Mivacurium is metabolized by plasma cholinesterase, atracurium is metabolized by plasma esterase, and both atracurium and cisatracurium undergo Hoffman elimination. The aminosteroids depend on organ function for metabolism and clearance, and some have active metabolites. Vecuronium and pancuronium undergo partial hepatic metabolism, and both have active metabolites. Rocuronium is not metabolized. Elimination of the aminosteroids is dependent on the kidney and liver to various degrees (Table 7-5).[53]

Table 7-5

Metabolism and Elimination of NMBDs

Drug	Metabolism	Metabolites	Elimination
Succinylcholine	Plasma cholinesterase (>98%)	Monoester, choline	Kidney (<2%)
Mivacurium	Plasma cholinesterase (>95%)	Monoester, quaternary alcohol	Kidney (<5%)
Atracurium	Plasma esterase, Hoffman elimination (60–90%)	Laudanosine, acrylates, alcohols, acids	Kidney (10–40%)
Cisatracurium	Hoffman elimination (77%)	Laudanosine, acrylates	Kidney (16%)
Rocuronium	None	None	Kidney(10–25%)
			Liver (>70%)
Vecuronium	Liver (30–40%)	3-OH vecuronium	Kidney (40–50%)
			Liver (50–60%)
Pancuronium	Liver (10–20%)	3-OH pancuronium	Kidney (85%)
			Liver (15%)

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SHORT-ACTING NONDEPOLARIZING NMBD

Mivacurium

Mivacurium is a short-acting benzylisoquinolinium that is hydrolyzed by plasma cholinesterase. Mivacurium is not available in the United States because production was discontinued in 2006, but the drug continues to be in use in Europe. It consists of three isomers, two of which are active. Compared to adults, infants and children have a higher ED95 for mivacurium. The ED95 in children is about 90 mcg/kg. An intubating dose of 0.25 mg/kg has an onset of 1.5 to 2 minutes, with complete recovery in 15 to 20 minutes.[54] Mivacurium undergoes degradation by plasma cholinesterase at a rate slower than that of succinylcholine. This may account for the longer duration of mivacurium compared to succinylcholine. Patients with decreased plasma cholinesterase activity will exhibit a prolonged duration of neuromuscular blockade with mivacurium.[55]

INTERMEDIATE-ACTING NONDEPOLARIZING NMBDS

Atracurium

Atracurium is an intermediate-acting benzylisoquinolinium consisting of 10 stereoisomers. Atracurium undergoes both spontaneous degradation and enzymatic hydrolysis. Under physiologic temperature and pH, atracurium is cleaved into inactive metabolites by the nonenzymatic Hofmann elimination reaction. Ester hydrolysis also occurs by nonspecific plasma esterases that are distinct from the plasma cholinesterase involved in degradation of succinylcholine. Thus, the duration of action of atracurium is not affected in patients with renal impairment, cirrhosis, or atypical plasma cholinesterase.[56] Laudanosine and acrylates are the major metabolites of atracurium from both degradation pathways. At high, nonclinical concentrations, laudanosine stimulates the central nervous system. The adverse effects of laudanosine are unlikely at clinically relevant doses of

atracurium.[57]

The ED95 of atracurium is higher in children (195 mcg/kg) than in neonates and infants (119 and 163 mcg/kg, respectively). With an intubating dose of 0.5 mg/kg, depression of twitch height by 95% occurs within 1 minute in neonates and infants and 1.4 minutes in children.[58] Recovery to 10% control twitch height occurs within 30 minutes in infants and children. Adverse effects with atracurium are related to histamine release, notably at higher doses. Hypotension, tachycardia, or bronchospasm can occur at doses greater than twice the ED95.

Cisatracurium

Cisatracurium is the *1R-Cis, 1′-R-Cis* stereoisomer of atracurium but unlike atracurium, cisatracurium does not undergo degradation by nonspecific esterases. Cisatracurium primarily undergoes Hofmann elimination. The organ-independent clearance of cisatracurium makes it an appropriate choice for patients with renal or hepatic dysfunction. Hofmann elimination of cisatracurium produces laudanosine and quaternary acrylates, which are inactive metabolites. As cisatracurium is more potent than atracurium, less laudanosine is produced at equipotent doses. Unlike atracurium, cisatracurium is not associated with significant histamine release.[59]

The ED95 of cisatracurium is similar in infants and children during nitrous oxide–narcotic anesthesia (43 and 47 mcg/kg, respectively).[60] After an intubating dose of 0.15 mg/kg, maximal blockade occurred at 2 minutes in infants and 3 minutes in children.[61] Time to recovery to 25% control twitch height was longer in infants compared to children (43.3 and 36.0 minutes, respectively). The rate of recovery is similar in infants and children. Due to its organ-independent clearance, cisatracurium is suitable for maintenance of neuromuscular blockade in the intensive care setting. In children receiving cisatracurium at a rate of 3.9 ± 1.3 mcg/kg/min, TOF ratio recovery of 70% occurred in 52 minutes on average.[62]

Rocuronium

Rocuronium is a monoquarternary aminosteroid NMBD of intermediate duration. The relative lower potency and consequent higher dose requirement of rocuronium compared to other NMBDs account for its more rapid onset of action at equipotent doses. The higher dose results in more drug molecules available to diffuse to the neuromuscular junction, thus hastening onset. A large dose (three to four times the ED95) of rocuronium can be used as an alternative to succinylcholine in situations where a rapid sequence induction is indicated. Rocuronium is not metabolized to any significant degree and is eliminated through hepatobiliary excretion in bile and feces. Approximately 10% is renally eliminated in urine. In cirrhosis or end-stage renal disease, the duration of action of rocuronium is prolonged.[63,64] A transient increase in heart rate can be observed at the higher dose range. It is unclear if the heart rate increase is due to pain on injection or a chronotropic effect.

The ED95 of rocuronium under nitrous oxide–opioid anesthesia in infants, children, and adults are 251, 409, and 350 mcg/kg, respectively.[65] A dose of 0.6 mg/kg provides intubating conditions within 1 minute in children 18 to 72 months.[66] A lower dose of 0.3 mg/kg provides intubating conditions in 95% of children 2 to 7 years within 2 minutes.[67] At this lower dose, recovery of TOF ratio to 0.8 was on average 24 minutes. In situations where rapid intubation is indicated, 1.2 mg/kg of rocuronium provides intubating conditions similar to 2 mg/kg of succinylcholine in children ages 2 to 10 years.[68] At 1.2 mg/kg in this age group, the time for 25% recovery of twitches is 41 minutes. In situations where intravenous access is unavailable, intramuscular rocuronium is an alternative, but the onset is slow and insufficient for emergencies. An intramuscular dose of 1 mg/kg in infants and 1.8 mg/kg in children provides ≥98% blockade in 7.4 and 8 minutes, respectively.[69] At 3 minutes, intubating conditions were inadequate for the majority of patients after an intramuscular dose.

Neonates and infants are more sensitive to the effects of rocuronium and require longer time to recovery than children and adolescents. Neonates and infants receiving 0.6 mg/kg rocuronium at 0 to 1 month, 2 to 4 months, and 5 to 12 months required 61, 49, and 44 minutes, respectively, for recovery to 25% control twitch height.[70] In comparison, 1- to 5-year-old children receiving the same dose (0.6 mg/kg) required 27 minutes for recovery to 25% of control twitch height.[71]

Vecuronium

Vecuronium, a derivative of pancuronium, was the first nondepolarizing NMBD with intermediate duration introduced into clinical use. Vecuronium is primarily eliminated in bile and urine. A portion also undergoes hepatic degradation into several metabolites. The 3-OH vecuronium metabolite has

about 60% the activity of vecuronium and undergoes renal clearance. In the pediatric intensive care setting, decreased clearance of vecuronium and its 3-OH metabolite may be responsible for prolonged neuromuscular blockade.[72] Patients with severe hepatic or renal dysfunction may have increased duration of action. Compared to the other aminosteroids, pancuronium and rocuronium, vecuronium does not have cardiovascular effects even at doses several times the ED95.[73]

The potency, onset, and duration of action of vecuronium vary between infants, children, and adolescents. Children have a higher dose requirement and shorter duration of action compared to neonates and adolescents. The ED95 is 47 mcg/kg in neonates and infants, 81 mcg/kg in children 3 to 10 years, and 55 mcg/kg in adolescents 13 years and older.[74] The onset of vecuronium is faster is infants compared to children and adolescents. In infants under 1, onset time after 0.1 mg/kg is 68 seconds, compared to 107 seconds in children 3 to 10 years old, and 93 seconds in children 10 to 15 years.[75] Overall, a dose of 0.1 mg/kg provides intubating conditions within 90 seconds in children 1 to 13 years.[76] Vecuronium can be considered a long-acting NMBD in patients under 1 year. A dose of 0.1 mg/kg produces >90% neuromuscular blockage from 57 to 60 minutes in children under 1 year, compared to 18 to 39 minutes in children ranging from 1 to 17 years.[77]

LONG-ACTING NONDEPOLARIZING NMBD

Pancuronium

Pancuronium is the only long-acting NMBD in clinical use. About 10% to 20% undergoes hepatic metabolism into three metabolites, the most important of which is 3-desacetylpancuronium which is about half as potent as pancuronium. Pancuronium is eliminated primarily by the kidney, with a small portion cleared by the liver. In the presence of severe hepatic or renal impairment, the duration of action is prolonged.[78,79] Pancuronium induces tachycardia due to a vagolytic effect at muscarinic receptors.[80] The vagolytic effect may be advantageous in infants, in whom bradycardia is not well tolerated. Pancuronium may also have a role in cardiac surgery, where the tachycardia may offset the bradycardia from high-dose opioids. Other effects include an increase in blood pressure and catecholamine release. Pancuronium does not produce histamine release.

The ED95 of pancuronium in infants is 45 to 52 mcg/kg in infants 3 to 12 months and 62 mcg/kg in children 13 to 83 months.[81] With a dose of 0.1 mg/kg, intubating conditions are good to excellent at 151 seconds in children 2 to 8 years.[82] The time to 25% twitch recovery at a dose of 0.12 mg/kg is 60 minutes in children 1 to 8 years.[83]

DRUG INTERACTIONS AND FACTORS AFFECTING NEUROMUSCULAR BLOCKADE

Various medications and factors can potentiate the effect of NMBDs.[84] Volatile inhaled anesthetics potentiate the effects of NMBDs and can reduce the dose requirement for maintenance of neuromuscular blockade. The exact mechanism is unknown but may be related to an effect at the acetylcholine receptor. In children 3 to 11 years old, the infusion rate of rocuronium to maintain greater than 90% twitch depression is reduced by 20% with halothane and isoflurane anesthesia, and by 50% with sevoflurane anesthesia.[85] Nitrous oxide appears to have minimal to no effect on neuromuscular blockade. Local anesthetics such as lidocaine enhance the effects of NMBDs. Antibiotics such as aminoglycosides, polymyxins, lincomycin, and clindamycin have minor effects in prolonging blockade. Magnesium decreases the onset of action and increases the duration of action of cisatracurium and rocuronium. Hypothermia prolongs the effect of NMBDs.

Resistance to the effects of nondepolarizing NMBDs can be observed in patients under long-term antiepileptic therapy. Rocuronium and vecuronium have a shorter duration of action in children on chronic carbamazepine and phenytoin therapy.[86,87] The effect of chronic anticonvulsant therapy on atracurium and cisatracurium is less apparent. Antiepileptics induce the cytochrome P450 system, which may account for more rapid clearance of the aminosteroid NMBDs. Calcium can decrease sensitivity to NMBDs.

ANTAGONISM OF NEUROMUSCULAR BLOCKING AGENTS

Adequate recovery from neuromuscular blockade must be present prior to extubation. Residual neuromuscular blockade increases the risk of perioperative complications such as hypoxemia and airway obstruction.[88] Recovery of respiratory muscle function may be especially important in infants and children due to their higher oxygen requirement. Clinical evaluation of muscle tone by the anesthesiologist may underestimate the degree

of residual neuromuscular blockade. The degree of recovery should be assessed prior to extubation and traditionally, a TOF ratio of 0.7 was considered adequate neuromuscular recovery. However, a TOF ratio <0.9 is associated with pharyngeal dysfunction, laryngeal aspiration, and airway obstruction.[89] There is abundant data that a TOF ratio of >0.9 is required for complete recovery. Administration of anticholinesterase for antagonism of neuromuscular blockade should be delayed until a TOF count of two or greater is present.[90] A portion of patients who receive neostigmine with a TOF count of 1 will have inadequate return of neuromuscular function at 20 minutes after reversal.[91]

There are two classes of agents for reversal of neuromuscular blockade: anticholinesterases and cyclodextrins.

Anticholinesterases

Anticholinesterases are agents that inhibit acetylcholinesterase. Inhibition of acetylcholinesterase prevents breakdown of ACh in the neuromuscular junction. ACh competes with a nondepolarizing NMBD for binding with the receptor. The increased concentration of ACh at the motor end plate alters the balance in favor of neuromuscular transmission.

The effects of increased ACh are not limited to the neuromuscular junction. Activation of muscarinic ACh receptors of the parasympathetic system can result in bradycardia, salivation, bronchospasm, increased gastrointestinal motility, and nausea and vomiting.[92] To counter the muscarinic effects, an antimuscarinic such as glycopyrrolate (5–10 mcg/kg) or atropine (10–20 mcg/kg) should be administered with an anticholinesterase.

The three anticholinesterases traditionally available for reversal of nondepolarizing NMBDs are edrophonium, neostigmine, and pyridostigmine. Among their differences is the time to onset. Edrophonium is the most rapid with peak effect within 2 minutes, while pyridostigmine is the slowest.[93] Although the rapid onset of edrophonium may be clinically useful, it is not as effective as neostigmine in antagonizing profound blockade of greater than 90% twitch suppression.[94] Compared to neostigmine, edrophonium has greater variability in individual patient response. Furthermore, the duration of action of edrophonium is shorter than that of neostigmine, such that there is a concern of recurarization, or a return of neuromuscular blockade after a period of recovery. Pyridostigmine, with a slower onset time than neostigmine, has fallen out of favor as a reversal agent. Neostigmine is the most commonly used anticholinesterase for antagonism of neuromuscular blockade and has been advocated as the anticholinesterase for use in pediatrics.[95]

Neostigmine

Neostigmine is a quaternary ammonium compound that forms a covalent bond with acetylcholinesterase. It is cleared by the kidney, such that clearance is prolonged in patients with severe renal disease. The time to onset is 5 to 10 minutes in infants, children, and adults.[96] The duration of action of approximately 1 to 2 hours is comparable between age groups. The elimination half-life is faster in infants compared with children and adults. The dose for reversal varies from 0.03 to 0.07 mg/kg. In infants and children with 90% twitch depression from atracurium, a dose of 0.05 mg/kg produces a TOF ratio of 0.9 or greater at 13 minutes, with neonates and infants under 1 year showing the fastest recovery.[90] In children 2 to 12 years and adults with 90% twitch depression from rocuronium, a dose of 0.07 mg/kg of neostigmine results in a TOF ratio of 0.9 or greater within 8 minutes, with children showing a shorter time to reversal.[97] When reversing patients with a low degree of residual blockade (such as the presence of four twitches and TOF ratio of 0.4–0.6), a smaller dose of 0.02 to 0.03 mg/kg of neostigmine may be adequate.[98]

Edrophonium

Edrophonium inhibits acetylcholinesterase by forming a reversible ionic bond. It is less potent than neostigmine and has a faster onset of action. A reversal dose of 0.5 to 1 mg/kg has an onset of action within 2 minutes.[88] In infants and children with 90% twitch depression from pancuronium, initial recovery of neuromuscular function was faster with edrophonium compared to neostigmine. Recovery is comparable at 10 minutes.[99] The effects of edrophonium are more variable than those of neostigmine, and the final TOF ratio reached is less with edrophonium compared to neostigmine.[90] Edrophonium is less effective at reversing profound neuromuscular blockade than neostigmine.[89]

Cyclodextrins

Sugammadex

Sugammadex is a γ-cyclodextrin that can reverse aminosteroid NMBDs. Sugammadex is an oligosaccharide arranged in a ring. Rocuronium, and to a lesser extent vecuronium and pancuronium, binds the center of the ring structure, forming a complex that is renally excreted.[100] Administration of 2 mg/kg sugammadex at the reappearance of the second twitch results in recovery to a TOF ratio of 0.9 within 0.6 minutes for infants and 1.2 minutes in children.[101] Recovery is faster in infants than in children and adults. Sugammadex has the ability to quickly reverse profound block from rocuronium. In adults, 16 mg/kg sugammadex given 3 minutes after 1.2 mg/kg rocuronium results in recovery to a TOF ratio of 0.9 within 3 minutes after administration of sugammadex.[102] In infants 2 to 12 months with a TOF ratio of 0 at the end of surgery, a dose of 3 mg/kg sugammadex results in a TOF ratio of >0.9 within 2 minutes.[103] The FDA initially deferred approval for sugammadex, requesting additional data on hypersensitivity, but granted approval in 2015.

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