Chapter

11 NEUROMUSCULAR BLOCKING DRUGS

Ronald D. Miller

Neuromuscular blocking drugs (NMBDs) interrupt transmission of nerve impulses at the neuromuscular junction (NMJ) and thereby produce paresis or paralysis of skeletal muscles. On the basis of electrophysiologic differences in their mechanisms of action and duration of action, these drugs can be classified as depolarizing NMBDs (mimic the actions of acetylcholine [ACh]) and nondepolarizing NMBDs (interfere with the actions of ACh), the latter of which are further subdivided into long-, intermediate-, and short-acting drugs (Box 11.1). Succinylcholine (SCh) is the only depolarizing NMBD used clinically. It is also the only NMBD that has both a rapid onset and ultrashort duration of action. Among the nondepolarizing NMBDs, rocuronium's rapid onset time most closely resembles that of SCh.

Box 11.1 Classification of Neuromuscular Blocking Drugs

Depolarizing (Rapid Onset and Ultrashort-Acting)
Succinylcholine

Nondepolarizing
Long-acting
- Pancuronium

Intermediate-acting
- Vecuronium
- Rocuronium
- Atracurium
- Cisatracurium

Short-acting
- Mivacurium

CLINICAL USES

The principal clinical uses of NMBDs are to produce skeletal muscle relaxation for facilitation of tracheal intubation and to provide optimal surgical working conditions. NMBDs may also be administered during cardiopulmonary resuscitation (also see Chapter 45) and to patients in emergency departments (also see Chapter 42) and intensive care units (also see Chapter 41) to facilitate mechanical ventilation of the patient's lungs. Of prime importance is to recognize that NMBDs lack analgesic or anesthetic effects and should not be used to render an inadequately anesthetized patient paralyzed. An inadequately anesthetized but paralyzed patient is a major risk for awareness during general anesthesia (see Chapter 47). Ventilation of the lungs must be mechanically provided whenever significant skeletal muscle weakness is produced by NMBDs. Clinically, intraoperative clinical evaluation of neuromuscular blockade is typically provided by visually monitoring the mechanical response (twitch response) produced by electrical stimulation of a peripheral nerve (usually a branch of the ulnar or facial nerve) delivered from a peripheral nerve stimulator (see the section, "Monitoring the Effects of Nondepolarizing Neuromuscular Blocking Drugs"). This chapter places increased emphasis on the value of monitoring by use of a peripheral nerve stimulator when NMBDs are given. Also, neostigmine has been the standard "reversal" drug for a nondepolarizing neuromuscular blockade; sugammadex is a relatively new reversal drug that has a unique mechanism of action and specifically reverses a rocuronium- and vecuronium-induced neuromuscular blockade.

Choice of Neuromuscular Blocking Drug

The choice of NMBD is influenced by its speed of onset, duration of action, route of elimination, and associated side effects, such as drug-induced changes in systemic arterial blood pressure, heart rate, or both. Rapid onset and brief duration of skeletal muscle paralysis, characteristic of SCh, are useful when tracheal intubation is the reason for administering an NMBD. Because of its rapid onset time, rocuronium is often used to facilitate tracheal intubation, but its duration of action is much longer than that of SCh. However, an approved indication for sugammadex is reversal of a profound neuromuscular blockade specifically from rocuronium or vecuronium. For example, if rocuronium were given to facilitate endotracheal intubation, but the trachea could not be intubated, sugammadex could reverse a profound neuromuscular blockade. Although SCh can be given intermittently, nondepolarizing NMBDs are usually selected when longer periods of neuromuscular blockade (e.g., more than 15 to 45 minutes) are needed. When rapid onset of skeletal muscle paralysis is not necessary, skeletal muscle relaxation can be induced by the administration of other long- or intermediate-acting nondepolarizing NMBDs to facilitate tracheal intubation.

Hypersensitivity Reactions

The overall incidence of life-threatening anesthetic-related hypersensitivity reactions ranges between 1/10,000 and 1/20,000 procedures and varies widely between countries.[1] Although antibiotics are likely the most common cause, NMBDs are the triggering drugs in 11% to 35% of these reactions. Rocuronium and SCh are the most common offenders. Even though it does not release histamine, rocuronium was identified as producing an increased risk for hypersensitivity reactions in France and Norway, with no confirmation from other countries. More recently, a follow-up study from Norway of 83 cases of anaphylaxis during general anesthesia revealed that 77% of these reactions were mediated by immunoglobulin E and 93% were associated with NMBDs, with SCh being the most common drug.[2] In an analysis of all allergic drugs used in anesthesia at the Mayo Clinic,[3] antibiotics were the most common cause, with NMBDs being second at 11% of the reactions. There may be cross-sensitivity among all NMBDs because of the presence of a common antigenic component, the quaternary ammonium group. Anaphylactic reactions after the first exposure to an NMBD may reflect sensitization from previous contact with cosmetics or soaps that also contain antigenic quaternary ammonium groups. Sugammadex (see the section, "Antagonism of Nondepolarizing Neuromuscular Blocking Drugs" later in this chapter) was recently approved by the Food and Drug Administration (FDA). The delay in sugammadex's approval was partly because of hypersensitivity concerns. The conclusion was that the most common signs of occasional cases of hypersensitivity were nausea and urticaria. However, sugammadex has been approved in Europe and other countries for several years. Treatment of a life-threatening hypersensitivity reaction requires immediate therapy including cardiopulmonary resuscitation and epinephrine (see Chapter 45 for details).

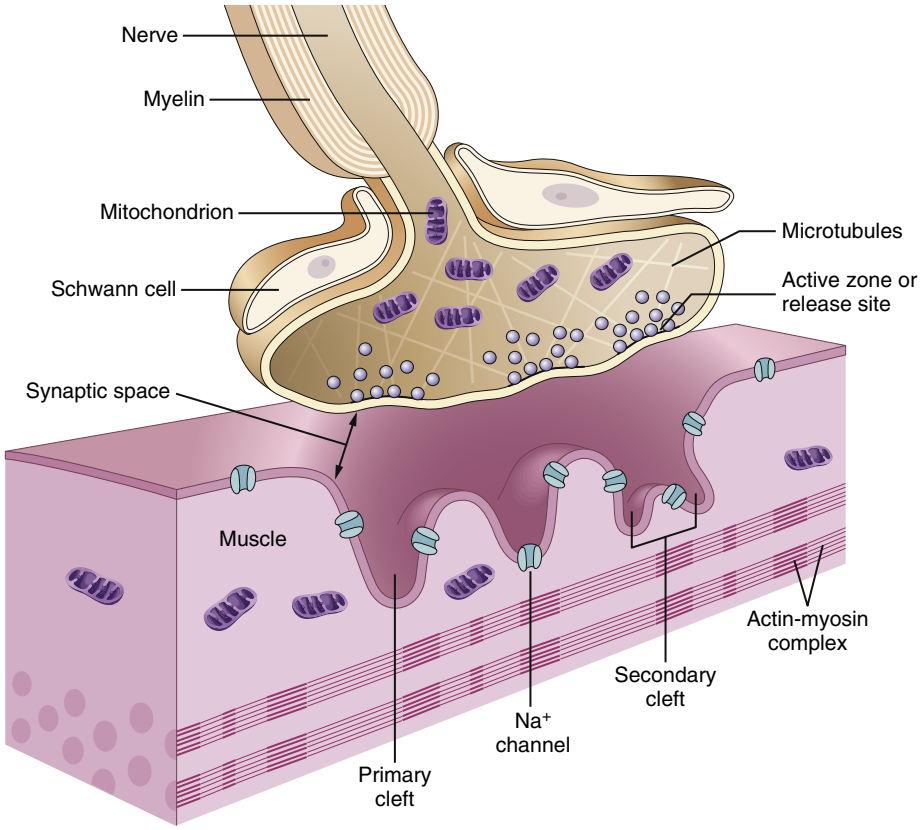

Fig. 11.1 Adult neuromuscular junction with the three cells that constitute the synapse: the motor neuron (i.e., nerve terminal), muscle fiber, and Schwann cell. The motor neuron from the ventral horn of the spinal cord innervates the muscle. Each fiber receives only one synapse. The motor nerve loses its myelin and terminates on the muscle fiber. The nerve terminal, covered by a Schwann cell, has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side and mitochondria and microtubules toward its other side. A synaptic gutter, made up of a primary and many secondary clefts, separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. Sodium channels are present at the clefts and throughout the muscle membrane. (From Martyn JAJ. Neuromuscular physiology and pharmacology. In Miller RD, ed. *Miller's Anesthesia.* 8th ed. Philadelphia: Elsevier Saunders; 2015.)

NEUROMUSCULAR JUNCTION

The anatomy of the NMJ consists of a prejunctional motor nerve ending separated from the highly folded postjunctional membrane of the skeletal muscle by a synaptic cleft (Fig. 11.1).[4] Nicotinic acetylcholine receptors (nAChRs) are located at pre- and postjunctional sites. Neuromuscular transmission is initiated by arrival of an impulse at the motor nerve terminal with an associated influx of calcium ions and resultant release of the ligand ACh. ACh binds to AChRs (the ligand-gated channel) on postjunctional membranes and thereby causes a change in membrane permeability to ions, principally potassium and sodium. This change in permeability and movement of ions causes a decrease in the transmembrane potential from about –90 mV to –45 mV (threshold potential), at which point a propagated action potential spreads over the surfaces of skeletal muscle fibers and leads to muscular contraction. ACh is rapidly hydrolyzed (within 15 ms) by the enzyme acetylcholinesterase (true cholinesterase), thus restoring membrane permeability (repolarization) and preventing sustained depolarization. Acetylcholinesterase is primarily located in the folds of the end-plate region, which places it in close proximity to the site of action of ACh.

Prejunctional Receptors and Release of Acetylcholine

ACh is synthesized in the motor nerve terminal, and the protein synapsin anchors the ACh vesicle to the release site of the terminal. Some of the ACh is then released,

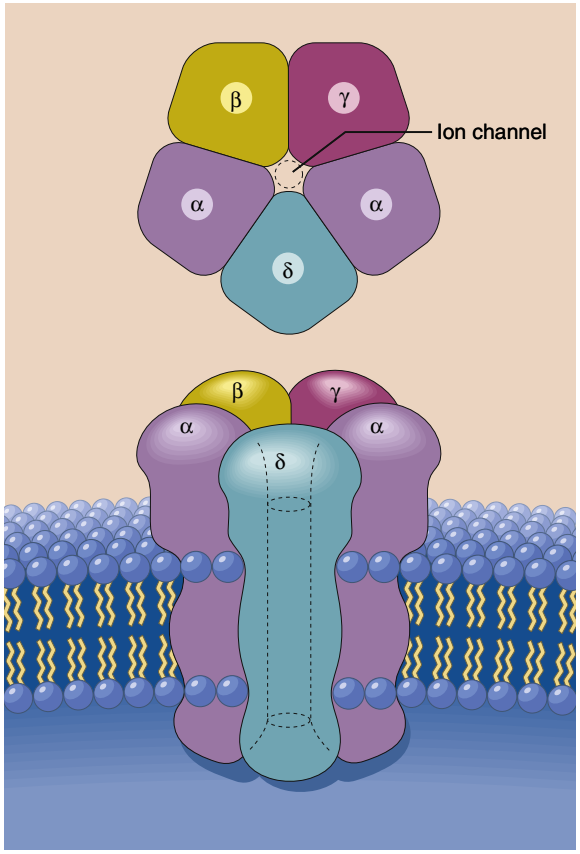

Fig. 11.2 The postjunctional nicotinic cholinergic receptor consists of five subunits (α, α, β, γ, δ) arranged to form an ion channel. (From Taylor P. Are neuromuscular blocking agents more efficacious in pairs? *Anesthesiology.* 1985;63:1-3, used with permission.)

and the rest is held in reserve for response to a stimulus. Presynaptic receptors, aided by calcium, facilitate replenishment of the motor nerve terminal, which can be stimulated by SCh and neostigmine and depressed by small doses of nondepolarizing NMBDs. Inhibition of these presynaptic nAChRs explains the fade in response to high-frequency repetitive stimulation such as tetanic or even train-of-four (TOF) stimulation.[4]

Postjunctional Receptors

Postjunctional receptors are glycoproteins consisting of five subunits (Fig. 11.2).[4] The subunits of the receptor are arranged such that a channel is formed that allows the flow of ions along a concentration gradient across cell membranes. This flow of ions is the basis of normal neuromuscular transmission. Extrajunctional receptors retain the two α-subunits but may have an altered γ- or δ-subunit by the substitution of an ε-unit.

The two α-subunits are the binding sites for ACh and are the sites occupied by NMBDs. For example, occupation of one or both α-subunits by a nondepolarizing NMBD causes the ion channel to remain closed, and ion flow to produce depolarization cannot occur. SCh attaches to α-sites and causes the ion channel to remain open (mimics ACh), thereby resulting in prolonged depolarization. Large doses of nondepolarizing NMBDs (large molecules) may also act to occlude the channel and in this way prevent the normal flow of ions. Neuromuscular blockade secondary to occlusion of the channels is resistant to drug-enhanced antagonism with anticholinesterase drugs. The lipid environment around cholinergic receptors can be altered by drugs such as volatile anesthetics, thus changing the properties of the ion channels. This probably accounts for the augmentation of neuromuscular blockade by volatile anesthetics.

Extrajunctional Receptors

Postjunctional receptors are confined to the area of the end plate precisely opposite the prejunctional receptors, whereas extrajunctional receptors (the ε-unit is replaced by γ-subunits) are present throughout skeletal muscles. Extrajunctional receptor synthesis is normally suppressed by neural activity. Prolonged inactivity, sepsis, and denervation or trauma (burn injury) to skeletal muscles may be associated with a proliferation of extrajunctional receptors. When activated, extrajunctional receptors stay open longer and permit more ions to flow, which in part explains the exaggerated hyperkalemic response when SCh is administered to patients with denervation or burn injury. Proliferation of these receptors also accounts for the resistance or tolerance to nondepolarizing NMBDs, as can occur with burns or prolonged (several days) immobilization (also see discussion under the section, "Hyperkalemia").[5,6]

STRUCTURE-ACTIVITY RELATIONSHIPS

NMBDs are quaternary ammonium compounds that have at least one positively charged nitrogen atom that binds to the α-subunit of postsynaptic cholinergic receptors (Fig. 11.3). In addition, these drugs have structural similarities to the endogenous neurotransmitter ACh. For example, SCh is two molecules of ACh linked by methyl groups. The long, slender, flexible structure of ACh allows it to bind to and activate cholinergic receptors. The bulky rigid molecules that are characteristic of nondepolarizing NMBDs, though containing portions similar to ACh, do not activate cholinergic receptors.

Nondepolarizing NMBDs are either aminosteroid compounds (pancuronium, vecuronium, rocuronium) or benzylisoquinolinium compounds (atracurium, cisatracurium, mivacurium). Pancuronium is the bisquaternary

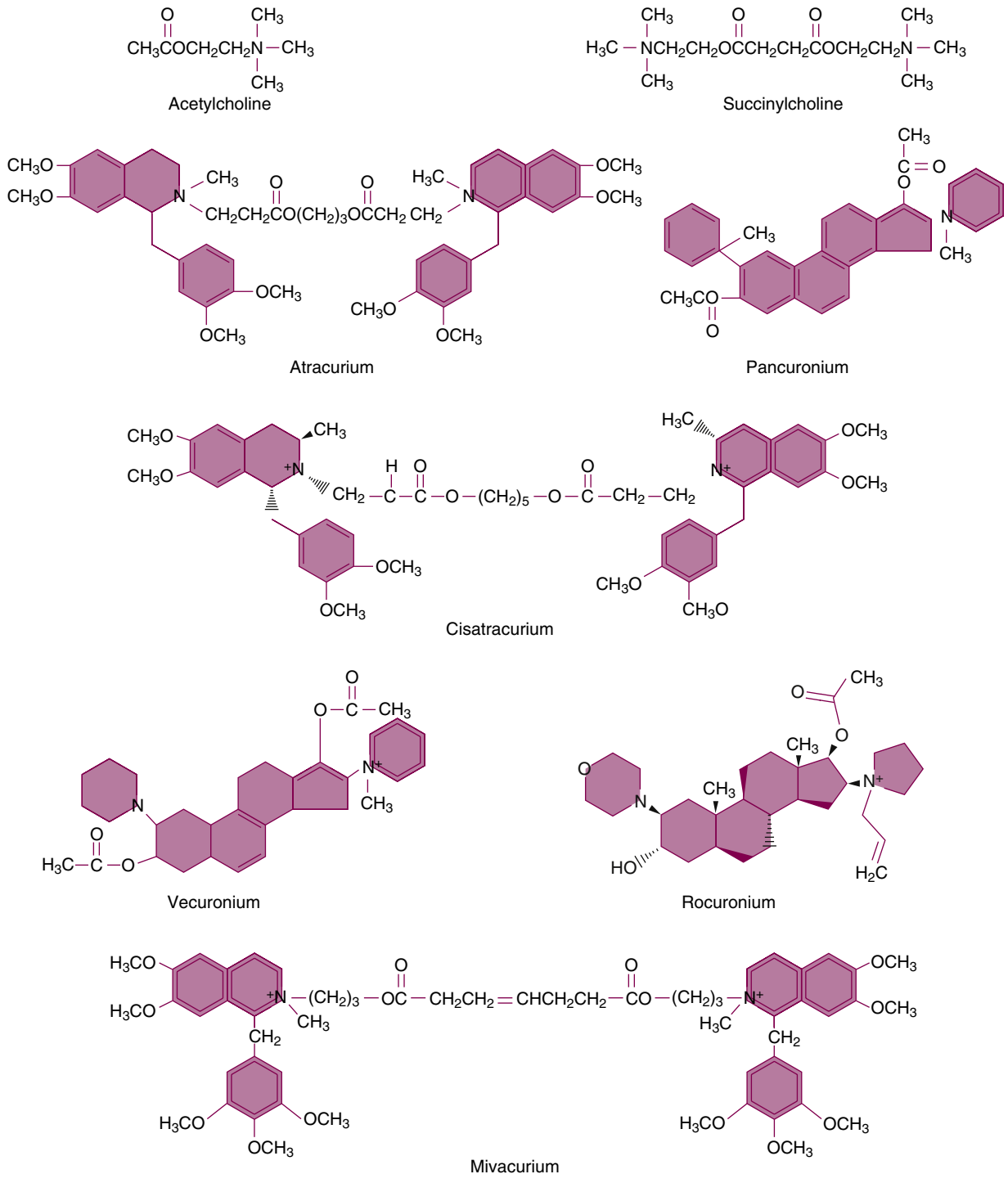

Fig. 11.3 Chemical structure of acetylcholine and neuromuscular blocking drugs.

aminosteroid NMBD most closely related to ACh structurally. The ACh-like fragments of pancuronium give the steroidal molecule its high degree of neuromuscular blocking activity. Vecuronium and rocuronium are monoquaternary analogs of pancuronium. Aminosteroid NMBDs lack hormonal activity. Benzylisoquinolinium derivatives are more likely than aminosteroid derivatives to evoke the release of histamine, presumably reflecting the presence of a tertiary amine.

DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

SCh is the only depolarizing NMBD used clinically. Furthermore, it is the only NMBD with both a rapid onset and ultrashort duration of action. Typically, doses of 0.5 to 1.5 mg/kg are administered intravenously and produce a rapid onset of skeletal muscle paralysis (30 to 60 seconds) that lasts 5 to 10 minutes because of its unique breakdown (Fig. 11.4). These characteristics make SCh ideal for providing rapid skeletal muscle paralysis to facilitate tracheal intubation. SCh has been used clinically for more than 60 years. Despite consistent industrial efforts, no drug has been developed that is better than SCh for tracheal intubation.[7] Although an intravenous dose of 0.5 mg/kg may be adequate, 1.0 to 1.5 mg/kg is commonly administered to facilitate tracheal intubation. If a subparalyzing dose of a nondepolarizing NMBD (pretreatment with 5% to 10% of its 95% effective dose [ED_{95}]) is administered 2 to 4 minutes before injection of SCh to blunt fasciculations, the dose of SCh should be increased by about 70%. Although ideal for facilitating tracheal intubation, SCh has many adverse effects (Box 11.2). As an alternative, the intermediate-acting nondepolarizing NMBD rocuronium has an onset time as rapid as SCh in doses ranging from 1.0 to 1.2 mg/kg.

Characteristics of Blockade

SCh mimics the action of ACh and produces a sustained depolarization of the postjunctional membrane. Skeletal muscle paralysis occurs because a depolarized postjunctional membrane and inactivated sodium channels cannot respond to subsequent release of ACh (hence, the designation depolarizing neuromuscular blockade). Depolarizing neuromuscular blockade is also referred to as *phase I blockade*. Phase II blockade is present when the postjunctional membrane has become repolarized but still does not respond normally to ACh (desensitization neuromuscular blockade). The mechanism of phase II blockade is unknown but may reflect the development of nonexcitable areas around the end plates that become repolarized but nevertheless prevent the spread of impulses initiated by the action of ACh. With the initial

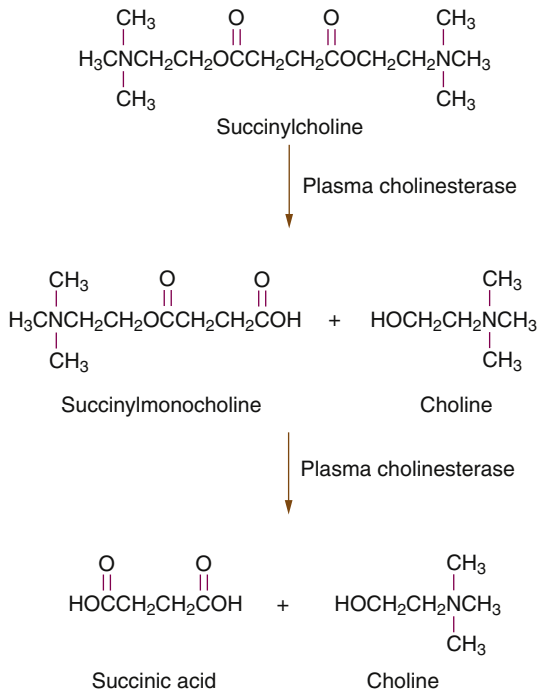

Fig. 11.4 The brief duration of action of succinylcholine is due to its rapid hydrolysis in plasma by cholinesterase enzyme to inactive metabolites (succinylmonocholine has 1/20 and 1/80 the activity of succinylcholine at the neuromuscular junction).

Box 11.2 Adverse Side Effects of Succinylcholine

- Cardiac dysrhythmias
  - Sinus bradycardia
  - Junctional rhythm
  - Sinus arrest
- Fasciculations
- Hyperkalemia
- Myalgia
- Myoglobinuria
- Increased intraocular pressure
- Increased intragastric pressure
- Trismus

dose of SCh, subtle signs of a phase II blockade begin to appear (fade to tetanic stimulation).[8] Phase II blockade, which resembles the blockade produced by nondepolarizing NMBDs, predominates when the intravenous dose of SCh exceeds 3 to 5 mg/kg (Table 11.1).

The sustained depolarization produced by the initial administration of SCh is initially manifested as transient generalized skeletal muscle contractions known as *fasciculations*. Furthermore, the sustained opening of sodium channels produced by SCh is associated with leakage of potassium from the interior of cells sufficient to increase plasma concentrations of potassium by about

Table 11.1 Comparison of Depolarizing (Succinylcholine) and Nondepolarizing (Rocuronium) Neuromuscular Blocking Drugs

	Succinylcholine		
Feature	**Phase I**	**Phase II**	**Rocuronium**
Administration of rocuronium	Antagonize	Augment	Augment
Administration of succinylcholine	Augment	Augment	Antagonize
Administration of neostigmine	Augment	Antagonize	Antagonize
Fasciculations	Yes		No
Response to single electrical stimulation (single twitch)	Decreased	Decreased	Decreased
Train-of-four ratio	>0.7	<0.3	<0.3
Response to continuous (tetanus) electrical stimulation	Sustained	Unsustained	Unsustained
Post-tetanic facilitation	No	Yes	Yes

Table 11.2 Variants of Plasma Cholinesterase and Duration of Action of Succinylcholine

Variants of Plasma Cholinesterase	Type of Buty butyrylcholinesterase/ TG Icholinesterase	Incidence	Dibucaine Number (% Inhibition of Enzyme Activity)	Duration of Succinylcholine-Induced Neuromuscular Blockade (min)
Homozygous, typical (usual, U)	UU	Normal	70-80	5-10
Heterozygous	UA	1/480	50-60	20
Homozygous, atypical (A)	AA	1/3200	20-30	60-180

0.1 to 0.4 mEq/L. With proliferation of extrajunctional nAChRs and damaged muscle membranes, many more channels will leak potassium and thereby lead to acute hyperkalemia.

Metabolism

Hydrolysis of SCh to inactive metabolites is accomplished by plasma cholinesterase (pseudocholinesterase) produced in the liver (see Fig. 11.4). Plasma cholinesterase has an enormous capacity to hydrolyze SCh at a rapid rate (ACh is metabolized even more rapidly by acetylcholinesterase) such that only a small fraction of the original intravenous dose reaches the NMJ. Because plasma cholinesterase is not present at the NMJ, the neuromuscular blockade produced by SCh is terminated by its diffusion away from the NMJ into extracellular fluid. Therefore, plasma cholinesterase influences the duration of action of SCh by controlling the amount of SCh that is hydrolyzed before reaching the NMJ. Liver disease must be severe before decreases in the synthesis of plasma cholinesterase are sufficient to prolong the effects of SCh. Potent anticholinesterases, as used in the treatment of myasthenia gravis, and certain chemotherapeutic drugs (nitrogen mustard, cyclophosphamide) may so decrease plasma cholinesterase activity that prolonged skeletal muscle paralysis follows the administration of SCh.

Atypical Plasma Cholinesterase

Atypical plasma cholinesterase lacks the ability to hydrolyze ester bonds in drugs such as SCh and mivacurium. The presence of this atypical enzyme is often recognized only after an otherwise healthy patient experiences prolonged skeletal muscle paralysis (>1hour) after the administration of a conventional dose of SCh or mivacurium. Subsequent determination of the dibucaine number permits diagnosis of the presence of atypical plasma cholinesterase. Dibucaine is an amide local anesthetic that inhibits normal plasma activity by about 80%, whereas the activity of atypical enzyme is inhibited by about 20% (Table 11.2). The dibucaine number reflects the quality of plasma cholinesterase (ability to metabolize SCh and mivacurium) and not the quantity of enzyme that is circulating in plasma. For example, decreases in plasma

Table 11.3 Autonomic Nervous System and Histamine-Releasing Effects of Neuromuscular Blocking Drugs

Drug[a]	Nicotinic Receptors at Autonomic Ganglia	Cardiac Postganglionic Muscarinic Receptors	Histamine Release
Succinylcholine	Modest stimulation	Modest stimulation	Minimal
Pancuronium	None	Modest blockade	None
Vecuronium	None	None	None
Rocuronium	None	None	None
Atracurium	None	None	Slight[b]
Cisatracurium	None	None	None
Mivacurium	None	None	Slight[b]

[a]At 95% effective dose (ED_{95}).
[b]Occurs only with doses estimated to be 2 to 3 × ED_{95}.

cholinesterase activity because of liver disease or anticholinesterases are often associated with a normal dibucaine number.

Adverse Side Effects

Adverse side effects after the administration of SCh are numerous and may limit or even contraindicate the use of this NMBD in certain patients (see Box 11.2). After 60 years of use, SCh continues to cause serious complications.[9,10] SCh usually should not be given to patients 24 to 72 hours after major burns, trauma, and extensive denervation of skeletal muscles because it may result in acute hyperkalemia and cardiac arrest.[5,6] Administration of SCh to apparently healthy boys with unrecognized muscular dystrophy has resulted in acute hyperkalemia and cardiac arrest. For this reason, the FDA has issued a warning against the use of SCh in children, except for emergency control of the airway.

Cardiac Dysrhythmias

Sinus bradycardia, junctional rhythm, and even sinus arrest may follow the administration of SCh. These responses reflect the action of SCh at cardiac postganglionic muscarinic receptors, where this drug mimics the normal effects of ACh (Table 11.3). Cardiac dysrhythmias are most likely to occur when a second intravenous dose of SCh is administered about 5 minutes after the first dose. Intravenous administration of atropine 1 to 3 minutes before SCh decreases the likelihood of these cardiac responses. Yet, atropine administered intramuscularly with the preoperative medication does not reliably protect against SCh-induced decreases in heart rate. The effects of SCh at autonomic nervous system ganglia also mimic the actions of the neurotransmitter ACh and may be manifested as ganglionic stimulation with associated increases in systemic blood pressure and heart rate (see Table 11.3).

Hyperkalemia

Administration of SCh can rapidly result in massive hyperkalemia, serious cardiac arrythmias, and even cardiac arrest.[5,6] In some patients, potassium levels can exceed 10 mEq/L. The classic conditions that lead to hyperkalemia after SCh include burns, trauma, and spinal cord or other major neurologic damage. Any time prolonged skeletal muscle inactivity (critical care) or extensive muscle damage exists, patients may be susceptible to hyperkalemia 48 hours after injury, and this is dependent on the development of extrajunctional, atypical receptors as previously described.[4-6] When muscle has returned to its normal state, hyperkalemia will not occur. However, the judgment as to the "normal" state of the muscle is a clinically difficult estimation. In addition, extrajunctional receptors and hyperkalemia will develop in any patient who is immobile (critical care patients) for several days if SCh is given. For example, cardiac arrest has occurred when SCh has been used for emergency endotracheal intubation in the intensive care unit. The use of SCh for urgent tracheal intubation is contraindicated or not allowed in many intensive care units. The duration of susceptibility to the hyperkalemic effects of SCh is unknown, but the risk is probably decreased 3 to 6 months after denervation injury. All factors considered, it might be prudent to avoid administration of SCh to any patient more than 24 hours after a burn injury, extensive trauma, or spinal cord transection or who may become an intensive care patient.

Even though they may have increased potassium levels, patients with renal failure are not susceptible to an exaggerated release of potassium, and SCh can be safely administered to these patients, unless they have uremic neuropathy.

Myalgia

Postoperative skeletal muscle myalgia, manifested particularly in the muscles of the neck, back, and abdomen, may follow the administration of SCh. Myalgia localized

to neck muscles may be described as a "sore throat" by the patient and incorrectly attributed to the previous presence of a tracheal tube. Young adults undergoing minor surgical procedures that permit early ambulation seem most likely to complain of myalgia. Unsynchronized contractions of skeletal muscle fibers (fasciculations) associated with generalized depolarization lead to myalgia. Prevention of fasciculations by prior administration of subparalyzing doses of a nondepolarizing NMBD (pretreatment) or lidocaine will decrease the incidence but not totally prevent myalgia.[11] Magnesium will prevent fasciculations but not myalgia. Nonsteroidal antiinflammatory drugs are effective in treating the myalgia.

Increased Intraocular Pressure

SCh causes a maximum increase in intraocular pressure 2 to 4 minutes after its administration. This increase in intraocular pressure is transient and lasts only 5 to 10 minutes. The mechanism by which SCh increases intraocular pressure is unknown, although contraction of extraocular muscles with associated compression of the globe may be involved. The concern that contraction of extraocular muscles could cause extrusion of intraocular contents in the presence of an open eye injury has resulted in the common clinical practice of avoiding the administration of SCh to these patients. This theory has never been substantiated and is challenged by the report of patients with an open eye injury in whom intravenous administration of SCh did not cause extrusion of globe contents.[12] Furthermore, there is evidence that contraction of extraocular muscles does not contribute to the increase in intraocular pressure that accompanies the administration of SCh.[13]

Increased Intracranial Pressure

Increases in intracranial pressure after the administration of SCh can occur but are of little or no concern.

Increased Intragastric Pressure

SCh causes unpredictable increases in intragastric pressure. When intragastric pressure does increase, it seems to be related to the intensity of fasciculations, thus emphasizing the potential value of preventing this skeletal muscle activity by prior administration of a subparalyzing dose of a nondepolarizing NMBD. An unproven hypothesis is that this increased intragastric pressure may cause passage of gastric fluid and contents into the esophagus and pharynx, with a subsequent risk for pulmonary aspiration.

Trismus

Incomplete jaw relaxation with masseter jaw rigidity after a halothane-SCh sequence is not uncommon in children (occurs in about 4.4% of patients) and is considered a normal response. In extreme cases this response may be so severe that the ability to mechanically open the patient's mouth is limited. The difficulty lies in separating the normal response to SCh from the masseter rigidity that may be associated with malignant hyperthermia. Because SCh is not recommended for use in children, except for emergency airway control, trismus is less of an issue.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Nondepolarizing NMBDs are classified clinically as long-, intermediate-, and short-acting (see Box 11.1). These drugs act by competing with ACh for α-subunits at the postjunctional nicotinic cholinergic receptors and preventing changes in ion permeability (see Fig. 11.2). As a result, depolarization cannot occur (hence, the designation *nondepolarizing neuromuscular blockade*), and skeletal muscle paralysis develops. Differences in onset, duration of action, rate of recovery, metabolism, and clearance influence the clinical decision to select one drug versus another (Table 11.4). For example, rocuronium has the most rapid onset time and minimal cardiovascular effects; cisatracurium is not dependent on the kidney for its elimination. Do these characteristics make rocuronium the choice for facilitating endotracheal intubation and cisatracurium for kidney transplantation? Yet, only vecuronium and, more important, rocuronium are antagonized by sugammadex (described later). These are a few of the variables that influence the choice of NMBD to be used for individual clinical situations.

Pharmacokinetics

Nondepolarizing NMBDs, because of their quaternary ammonium groups, are highly ionized, water-soluble compounds at physiologic pH and possess limited lipid solubility. As a result, these drugs cannot easily cross lipid membrane barriers, such as the blood-brain barrier, renal tubular epithelium, gastrointestinal epithelium, or placenta. Therefore, nondepolarizing NMBDs do not produce central nervous system effects, renal tubular reabsorption is minimal, oral administration is ineffective, and maternal administration does not adversely affect the fetus. Redistribution of nondepolarizing NMBDs also exerts a role in the pharmacokinetics of these drugs.

Many of the variable pharmacologic responses of patients to nondepolarizing NMBDs can be explained by differences in pharmacokinetics, which can be changed by many factors, such as hypovolemia, hypothermia, and the presence of hepatic or renal disease (or both). Renal and hepatic elimination is aided by access to a large fraction of the administered drug because of the high degree of ionization, which maintains high plasma concentrations of nondepolarizing NMBDs and also prevents renal reabsorption of excreted drug.

Table 11.4 Comparative Pharmacology of Nondepolarizing Neuromuscular Blocking Drugs

Drug	ED_{95} (mg/kg)	Onset to Maximum Twitch Depression (min)	Duration to Return to ≥25%[a]	Intubating Dose (mg/kg)	Continuous Infusion (mg/kg/min)	Renal Excretion (% Unchanged)	Hepatic Degradation (%)	Biliary Excretion (% Unchanged)	Hydrolysis in Plasma
Pancuronium	0.07	3-5	60-90	0.1		80	10	5-10	No
Vecuronium	0.05	3-5	20-35	0.08-0.1	1	15-25	20-30	40-75	No
Rocuronium	0.3	1-2	20-35	0.6-1.2		10-25	10-20	50-70	No
Atracurium	0.2	3-5	20-35	0.4-0.5	6-8	NS	NS	NA	Enzymatic, spontaneous
Cisatracurium	0.05	3-5	20-35	0.1	1-1.5	NS	NS	NS	Spontaneous
Mivacurium	0.08	2-3	12-20	0.25	5-6	NS	NS	NS	Enzymatic

[a]Control twitch height (minutes).
ED_{95}, 95% effective dose; *NS*, not significant.

Renal disease markedly alters the pharmacokinetics of only the long-acting nondepolarizing NMBDs, such as pancuronium. The intermediate-acting NMBDs are eliminated by the liver (rocuronium), by metabolism by plasma cholinesterase (mivacurium), by Hofmann elimination (atracurium or cisatracurium), or by a combination of these mechanisms. The new reversal drug sugammadex is not recommended in patients with "severe" renal impairment.

Pharmacodynamic Responses

Enhancement of neuromuscular blockade by volatile anesthetics reflects a pharmacodynamic action as manifested by decreased plasma concentrations of nondepolarizing NMBDs required to produce a given degree of neuromuscular blockade in the presence of volatile anesthetics. In addition to volatile anesthetics, other drugs, such as aminoglycoside antibiotics, local anesthetics, cardiac antiarrhythmic drugs, dantrolene, magnesium, lithium, and tamoxifen (an antiestrogenic drug), may enhance the neuromuscular blockade produced by nondepolarizing NMBDs. A few drugs may diminish the effects of a nondepolarizing NMBD, including calcium, corticosteroids, and anticonvulsant (phenytoin) drugs. Some neuromuscular diseases can be associated with altered pharmacodynamic responses (myasthenia gravis, Duchenne muscular dystrophy). Burn injury causes resistance to the effects of nondepolarizing NMBDs, as reflected by the need to establish a higher plasma concentration of drug to achieve the same pharmacologic effect as in patients without a burn injury. There is resistance to the effects of nondepolarizing NMBDs in skeletal muscles affected by a cerebrovascular accident, perhaps reflecting proliferation of extrajunctional receptors that respond to ACh.

Cardiovascular Effects

Nondepolarizing NMBDs may exert minor cardiovascular effects through drug-induced release of histamine, effects on cardiac muscarinic receptors, or effects on nicotinic receptors at autonomic ganglia (see Table 11.4). Transient hypotension can occur with atracurium and mivacurium but usually with large doses (>0.4 and 0.15 mg/kg, respectively). The relative magnitude of the circulatory effects varies from patient to patient and depends on factors such as underlying autonomic nervous system activity, blood volume status, preoperative medication, drugs administered for maintenance of anesthesia, and concurrent drug therapy.

Critical Care Medicine and Critical Illness Myopathy and Polyneuropathy[14,15]

Currently, NMBDs are not used as often as in the past. Yet a small fraction of patients with asthma (receiving corticosteroids) or acutely injured patients with multiple organ system failure (including sepsis) who require mechanical ventilation of the lungs for prolonged periods (usually more than 6 days) may manifest prolonged skeletal

muscle weakness on recovery that is augmented by the skeletal muscle paralysis produced by NMBDs. These patients exhibit moderate to severe quadriparesis with or without areflexia, but they usually retain normal sensory function. The time course of the weakness is unpredictable, and in some patients the weakness may progress and persist for weeks or months. The pathophysiology of this myopathy is not well understood. Therefore, NMBDs should be given for 2 days or less and only after the use of analgesics, sedatives, and adjustments to ventilator settings have been maximally used. Although myopathy occurs autonomously, administration of NMBDs can augment the severity of this condition. SCh probably should not be used to facilitate endotracheal intubation in critically ill patients because of reports of cardiac arrest, presumably caused by acute hyperkalemia. In fact, SCh is not allowed for use in many critical care units.

LONG-ACTING NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUG

Pancuronium

Pancuronium is a bisquaternary aminosteroid nondepolarizing NMBD with an ED_{95} of 70 μg/kg; it has an onset of action of 3 to 5 minutes and a duration of action of 60 to 90 minutes (see Table 11.4 and Fig. 11.3). An estimated 80% of a single dose of pancuronium is eliminated unchanged in urine. In the presence of renal failure, plasma clearance of pancuronium is decreased 30% to 50%, thus resulting in a prolonged duration of action. An estimated 10% to 40% of pancuronium undergoes hepatic deacetylation to inactive metabolites, with the exception of 3-desacetylpancuronium, which is approximately 50% as potent as pancuronium at the NMJ.

Cardiovascular Effects

Pancuronium typically produces a modest 10% to 15% increase in heart rate, mean arterial pressure, and cardiac output. The increase in heart rate reflects pancuronium-induced selective blockade of cardiac muscarinic receptors (atropine-like effect), principally in the sinoatrial node. Histamine release and autonomic ganglion blockade are not produced by pancuronium.

INTERMEDIATE-ACTING NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Rocuronium, vecuronium, atracurium, and cisatracurium are classified as intermediate-acting nondepolarizing NMBDs. In contrast to the long-acting nondepolarizing NMBD pancuronium, these drugs possess efficient clearance mechanisms that create a shorter duration of action.

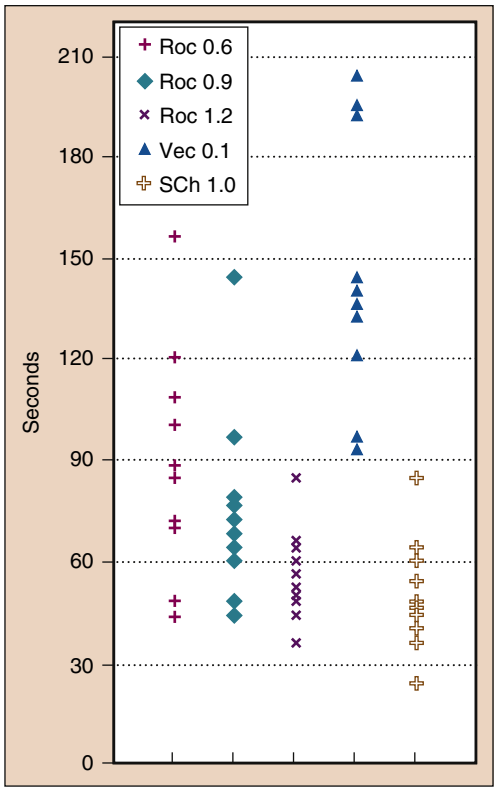

Fig. 11.5 The onset of maximum twitch depression is similar after the intravenous administration of rocuronium (Roc) at doses of 0.9 mg/kg and 1.2 mg/kg; succinylcholine (Sch) at 1.0 mg/kg; and vecuronium (Vec) at 0.1 mg/kg. (From Magorian TT, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology.* 1993;79:913-918, used with permission.)

When compared with pancuronium, these drugs have (1) a similar onset of maximum neuromuscular blockade, with the exception of rocuronium, which is unique because of its rapid onset, which can (with large doses) parallel that of SCh; (2) approximately one third the duration of action (hence the designation *intermediate acting*); (3) a 30% to 50% more rapid rate of recovery; and (4) minimal to absent cardiovascular effects except for atracurium. Neostigmine or sugammadex (only rocuronium and vecuronium) antagonism of the neuromuscular blockade produced by intermediate-acting nondepolarizing NMBDs is facilitated by the concomitant spontaneous recovery that occurs after rapid clearance of the drug.

Vecuronium

Vecuronium is a monoquaternary aminosteroid nondepolarizing NMBD with an ED_{95} of 50 μg/kg that produces an onset of action of 3 to 5 minutes and a duration of action of 20 to 35 minutes (see Fig. 11.3 and Table 11.4). This

drug undergoes both hepatic and renal excretion. Metabolites are pharmacologically inactive, with the exception of 3-desacetylvecuronium, which is approximately 50% to 70% as potent as the parent compound. The increased lipid solubility of vecuronium as compared with pancuronium also facilitates biliary excretion of vecuronium. The effect of renal failure on the duration of action of vecuronium is small, but repeated or large doses may result in prolonged neuromuscular blockade. Vecuronium is typically devoid of circulatory effects, emphasizing its lack of vagolytic effects (pancuronium) or histamine release (atracurium).

Rocuronium

Rocuronium is a monoquaternary aminosteroid nondepolarizing NMBD with an ED_{95} of 0.3 mg/kg that has an onset of action of 1 to 2 minutes and a duration of action of 20 to 35 minutes (see Table 11.4 and Fig. 11.3). The lack of potency of rocuronium in comparison to vecuronium is an important factor in determining the rapid onset of neuromuscular blockade produced by this NMBD. Conceptually, when a large number of molecules are administered, the result is a larger number of molecules that are available to diffuse to the NMJ. Thus, a rapid onset of action is more likely to be achieved with a less potent drug such as rocuronium. The onset of maximum single twitch depression after the intravenous administration of rocuronium at 3 to 4 × ED_{95} (1.2 mg/kg) resembles the onset of action of SCh after the intravenous administration of 1 mg/kg (Fig. 11.5).[16] However, the large doses of rocuronium (3 to 4 × ED_{95}) needed to mimic the onset time of SCh produce a duration of action resembling that of pancuronium.[17]

Clearance of rocuronium is largely as an unchanged drug in bile, with deacetylation not occurring. Renal excretion of the drug may account for as much as 30% of a dose, and administration of this drug to patients in renal failure could result in a longer duration of action, especially with repeated doses or prolonged intravenous infusion.

Atracurium

Atracurium is a bisquaternary benzylisoquinolinium nondepolarizing NMBD (mixture of 10 stereoisomers) with an ED_{95} of 0.2 mg/kg that produces an onset of action of 3 to 5 minutes and a duration of action of 20 to 35 minutes (see Table 11.4 and Fig. 11.3). Clearance of this drug is by a chemical mechanism (spontaneous nonenzymatic degradation at normal body temperature and pH known as Hofmann elimination) and a biologic mechanism (ester hydrolysis by nonspecific plasma esterases). Laudanosine is the major metabolite of both pathways. This metabolite is not active at the NMJ but may, in high, nonclinical concentrations, cause central nervous system stimulation. The two routes of metabolism occur simultaneously and are independent of hepatic and renal function, as well as plasma cholinesterase activity. As such, the duration of atracurium-induced neuromuscular blockade is similar in normal patients and those with absent or impaired renal or hepatic function or those with atypical plasma cholinesterase (emphasizes that ester hydrolysis of atracurium is unrelated to the plasma cholinesterase responsible for the hydrolysis of SCh and mivacurium). Ester hydrolysis accounts for an estimated two thirds of degraded atracurium. Hofmann elimination (also known as *exhaustive methylation*) accounts for the remaining breakdown of atracurium.

Cardiovascular Effects

Because of histamine release with larger doses, atracurium can cause hypotension and tachycardia. However, doses smaller than 2 × ED_{95} rarely cause cardiovascular effects.

Cisatracurium

Cisatracurium is a benzylisoquinolinium nondepolarizing NMBD with an ED_{95} of 50 μg/kg that has an onset of action of 3 to 5 minutes and a duration of action of 20 to 35 minutes (see Table 11.4 and Fig. 11.3).[18] Structurally, cisatracurium is an isolated form of 1 of the 10 stereoisomers of atracurium. This drug principally undergoes degradation by Hofmann elimination. In contrast to atracurium, nonspecific plasma esterases do not seem to be involved in the clearance of cisatracurium. The organ-independent clearance of cisatracurium means that this nondepolarizing NMBD, like atracurium, can be administered to patients with renal or hepatic failure without a change in its duration of action. Cisatracurium is often used in patients undergoing renal transplantation. Cisatracurium, in contrast to atracurium, is devoid of histamine-releasing effects, so cardiovascular changes do not accompany the rapid intravenous administration of even large doses of cisatracurium.

SHORT-ACTING NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUG

Mivacurium

Mivacurium is a benzylisoquinolinium nondepolarizing NMBD with an ED_{95} of 80 μg/kg that has an onset of action of 2 to 3 minutes and a duration of action of 12 to 20 minutes (see Table 11.4 and Fig. 11.3). As such, the duration of action of mivacurium is approximately twice that of SCh and 30% to 40% that of the intermediate-acting nondepolarizing NMBDs. Mivacurium consists of three stereoisomers, with the two most active isomers undergoing hydrolysis by plasma cholinesterase at a rate equivalent to 88% that of SCh. Hydrolysis of these two

isomers is responsible for the short duration of action of mivacurium. As with SCh, hydrolysis of mivacurium is decreased and its duration of action increased in patients with atypical plasma cholinesterase (see Table 11.2). Mivacurium is currently not being marketed in the United States and not available for delivering anesthetic care.

MONITORING THE EFFECTS OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Evaluation of the mechanically evoked responses produced by electrical stimulation delivered from a peripheral nerve stimulator is the most reliable method to monitor the pharmacologic effects of NMBDs. Use of a peripheral nerve stimulator permits titration of the NMBD to produce the desired pharmacologic effect, and at the conclusion of surgery the responses evoked by the nerve stimulator are used to judge spontaneous recovery from an NMBD-induced neuromuscular blockade, which is facilitated by the administration of anticholinesterase drugs (e.g., neostigmine or sugammadex) (see the discussion under "Antagonism of Nondepolarizing Neuromuscular Blocking Drugs").

Routine monitoring of neuromuscular function and blockade is strongly recommended by all experts in the field[19] and supported by large epidemiologic studies[20] and various safety organizations such as the Anesthesia Patient Safety Foundation (APSF). Yet monitoring of the neuromuscular blockade from NMBDs surprisingly is not routinely used during administration of anesthesia. Most surveys have found that only 30% to 70% of anesthesiologists in the United States and Europe use peripheral nerve stimulation as a monitor. Yet such monitoring allows NMBDs to be given in a more efficacious manner. Monitoring also provides a more precise guide for NMBD requirements intraoperatively and for the effective antagonism by neostigmine or sugammadex. More recently, complications in the postanesthesia care unit (PACU) have been documented to be less frequent when monitoring is used.

Even though not consistently done, monitoring the effects of NMBDs should be routinely performed.[21] As with many other monitors (e.g., pulse oximetry, see Chapter 20), perhaps using objective monitoring (i.e., peripheral nerve stimulation) will become mandatory. No matter which pattern of peripheral nerve stimulation is used, clinical care will be improved if such monitoring is used. Despite the presence of studies designed to establish the relative efficacy of different types of stimulation,[22] the type of stimulation being used is of secondary importance. Nevertheless, the well-informed clinician should have some basic knowledge of the various types of stimulation proposed and used. Furthermore, the various types of stimulation have varying sensitivity with the degree of neuromuscular blockade detected (Table 11.5). Conceptually, the question that can be asked is, "How many receptors can be still occupied and have a normal response to that particular pattern of stimulation?" When the pattern of stimulation requires more receptors to be unoccupied in order to have a normal response, then that approach will be more sensitive in detecting residual neuromuscular blockade. Now the technical aspects of monitoring of neuromuscular blockade will be described.

Most often, superficial electrodes or subcutaneous needles (must have a metal hub) are placed over the ulnar nerve at the wrist or elbow or the facial nerve on the lateral aspect of the face, and a supramaximal electrical stimulus is delivered from the peripheral nerve stimulator.[23,24] The adductor pollicis muscle is innervated solely by the ulnar nerve, which accounts for the popularity of placing stimulating electrodes from the peripheral nerve stimulator over the ulnar nerve. Facial nerve stimulation and observation of the orbicularis oculi muscle, though difficult to quantitate, may be a consideration when mechanically evoked

Table 11.5 Choice of Anticholinesterase Drug

TOF Visible Twitches	Estimated TOF Fade	Anticholinesterase Drug and Dose (mg/kg IV)	Anticholinergic Drug and Dose (μg/kg IV)[a]
None[b]		Not recommended	Not recommended
≤2	++++	Neostigmine 0.07	Glycopyrrolate 7 or atropine 15
3-4	+++	Neostigmine 0.04	Glycopyrrolate 7 or atropine 15
4	++	Edrophonium 0.5	Atropine 7
4	0	Edrophonium 0.25	Atropine 7

[a]Administered simultaneously with an anticholinesterase drug.
[b]Postpone drug-assisted antagonism until some evoked response is visible.
++++, Marked; +++, moderate; ++, minimal; *0*, none; *IV*, intravenous; *TOF*, train-of-four.
Modified from Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology*. 1992;77:785-792, used with permission.

responses to stimulation of the ulnar nerve are not visible because of positioning of the upper extremities.[25] Another consideration is the observation that monitoring the response of the orbicularis oculi muscle to facial nerve stimulation more closely reflects the onset of neuromuscular blockade at the larynx than does the response of the adductor pollicis to ulnar nerve stimulation (Fig. 11.6).[26] Moreover, the onset of neuromuscular blockade after the administration of nondepolarizing NMBDs is more rapid but less intense at the laryngeal muscles (vocal cords) than at the peripheral muscles (adductor pollicis) (see Fig. 11.5).[25] In this regard, the period of laryngeal paralysis may be dissipating before a maximum effect is reached at the adductor pollicis. In contrast, the onset of neuromuscular blockade at the laryngeal muscles and at the muscles innervated by the ulnar nerve is similar when SCh is administered. Thus, monitoring the twitch response at the adductor pollicis is more likely to parallel the intensity of the drug-induced effect at the laryngeal adductors when SCh is administered.

Patterns of Stimulation

Mechanically evoked responses used for monitoring the effects of NMBDs include the single twitch response, TOF ratio, double burst stimulation, tetanus, and post-tetanic stimulation (Figs. 11.6 to 11.10).[23,24] These mechanically evoked responses are evaluated visually, manually by touch (tactile), or by recording. The depth of neuromuscular blockade may be defined as the percentage of a predetermined inhibition of twitch response from control height (ED_{95}, dose necessary to depress the twitch

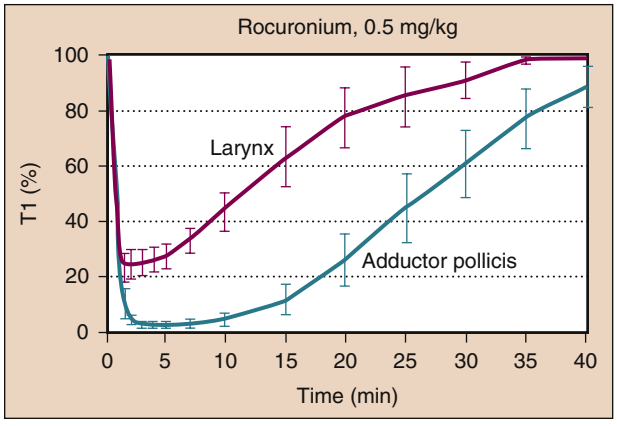

Fig. 11.6 The effects of rocuronium (in terms of maximum depression of the single twitch [T1] response) are less intense and the duration of action is less at the adductor muscles of the larynx than at the adductor pollicis. (From Meistelman C, Plaud B, Donati F. Rocuronium [ORG 9426] neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. *Can J Anaesth.* 1992;39:665-669, used with permission.)

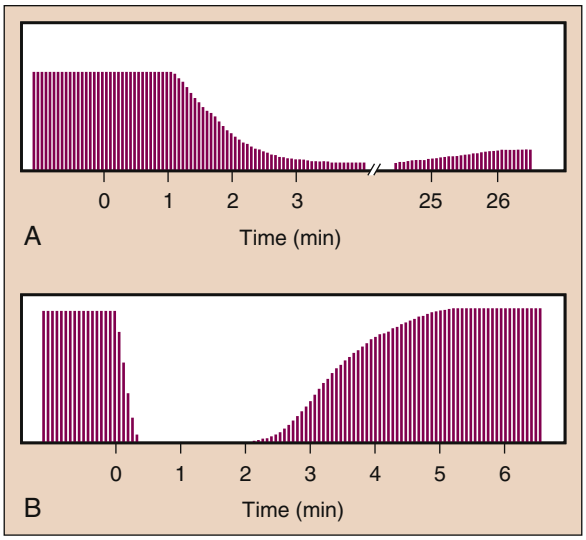

Fig. 11.7 Schematic illustration of the onset and recovery from the neuromuscular blocking effects of a nondepolarizing (A) or a depolarizing (B) neuromuscular blocking drug ("0 time" indicates injection of the neuromuscular blocking drug) as depicted by the mechanically evoked single twitch response to repeated electrical stimulation of the nerve. (Modified from Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *Br J Anaesth.* 1982;54:209-223, used with permission.)

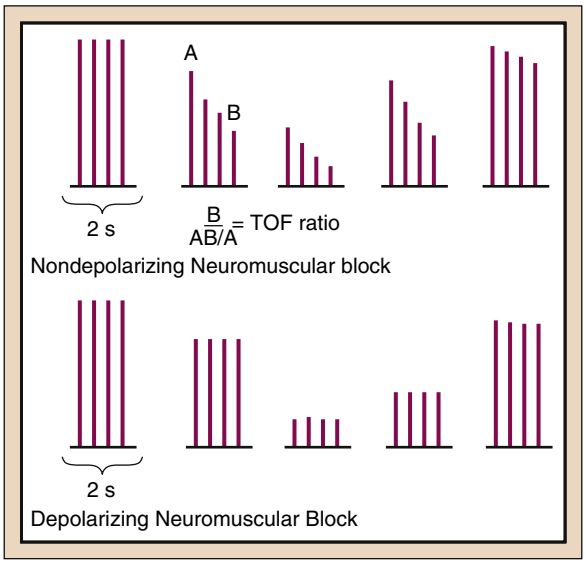

Fig. 11.8 Schematic illustration of the mechanically evoked response to train-of-four (TOF) electrical stimulation of the nerve after injection of a nondepolarizing neuromuscular blocking drug (upper panel) or a depolarizing (succinylcholine) neuromuscular blocking drug (lower panel). The TOF ratio, given by the relation of the first response (upper panel) to the fourth (lower panel), is less than 1 (fades) only in the presence of (upper panel) effects at the neuromuscular junction produced by a nondepolarizing neuromuscular blocking drug. (Modified from Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *Br J Anaesth.* 1982;54:209-223, used with permission.)

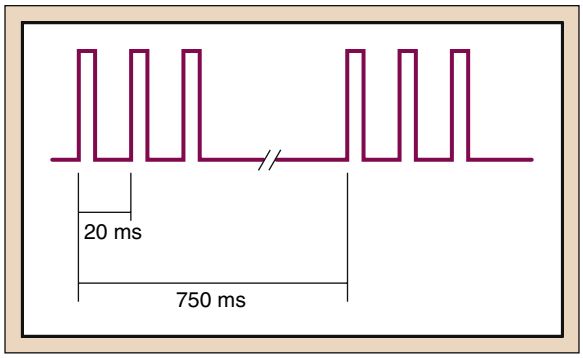

Fig. 11.9 Schematic illustration of the stimulation pattern of double burst stimulation (three electrical impulses at 50 Hz separated by 750 ms). (From Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology.* 1992;77:785-792, used with permission.)

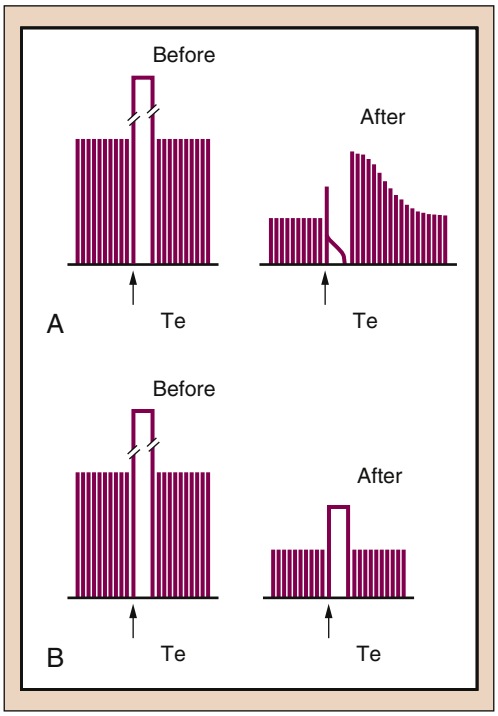

Fig. 11.10 Schematic illustration of the evoked response to tetanic (Te) stimulation (50 Hz for 5 seconds) before and after the intravenous injection of a nondepolarizing neuromuscular blocking drug (A) or a depolarizing (succinylcholine) neuromuscular blocking drug (B). (Modified from Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *Br J Anaesth.* 1982;54:209-223, used with permission.)

response 95%) and the duration of drug effect as the time from drug administration until the twitch response recovers to a percentage of control height (see Table 11.4).

The response to peripheral nerve stimulation can be used to answer the following questions:

1. Is the neuromuscular blockade adequate for surgery?
2. Is the neuromuscular blockade excessive?
3. Can this neuromuscular blockade be antagonized?

Depression of the twitch response greater than 90% or elimination of two to three twitches of the TOF correlates with acceptable skeletal muscle relaxation for performance of intra-abdominal surgery in the presence of an adequate concentration of volatile anesthetic. If all twitches from TOF stimulation are absent, more NMBD should not be given until some twitch is present. If some of the twitches from TOF stimulation are present, antagonism is likely to be successful (see the section, "Antagonism of Nondepolarizing Neuromuscular Blocking Drugs").

Train-of-Four Stimulation

TOF stimulation (four electrical stimulations at 2 Hz delivered every 0.5 second) is based on the concept that ACh is depleted by successive stimulations. Only four twitches are necessary because subsequent stimulation fails to further alter the release of additional ACh. In the presence of effects produced at the NMJ by nondepolarizing NMBDs, the height of the fourth twitch is lower than that of the first twitch, thereby allowing calculation of a TOF ratio (fade) (see Fig. 11.8).[23] Recovery of the TOF ratio to greater than 0.7 correlates with complete return to control height of a single twitch response. In the presence of effects produced at the NMJ by SCh, the TOF ratio remains near 1.0 because the height of all four twitch responses is decreased by a similar amount (phase I blockade) (see Fig. 11.8).[23] A TOF ratio of less than 0.3 in the presence of SCh reflects phase II blockade (see Table 11.1).

Double Burst Stimulation

Accurate estimation of the TOF ratio is not reliable clinically by either visual or manual assessment. Difficulty in estimating the TOF ratio may be due to the fact that the two middle twitch responses interfere with comparison of the first and last twitch response. In this regard, double burst stimulation (two bursts of three electrical stimulations separated by 750 ms) is perceived by the observer as two separate twitches (see Fig. 11.9).[24] The observer's ability to detect a TOF ratio less than 0.3 is improved with double burst stimulation, but the ability to conclude that the TOF ratio is greater than 0.7 is still not ensured.[27] In contrast to the difficulty in quantifying the TOF ratio, determination of the number of electrically evoked twitch responses to TOF stimulation is more likely to be reproducible. For example, the fourth twitch can be observed when the first twitch is equivalent to 30% to 40% of control twitch height, which corresponds to a TOF ratio of about 0.35. Counting the number of visible TOF responses may be helpful in predicting the ease with which neuromuscular blockade can be antagonized

Table 11.6 Clinical Tests of Neuromuscular Transmission

Test	Normal Function	% of Receptors Occupied[a]	Comment
Tidal volume	5 mL/kg	80	Insensitive
Train-of-four	No fade	70	Somewhat uncomfortable
Vital capacity	At least 20 mL/kg	70	Requires patient cooperation
Sustained tetanus (50 Hz)	No fade	60	Uncomfortable
Double burst stimulation	No fade	60	Uncomfortable
Head lift	180 degrees for 5 s	50	Requires patient cooperation
Handgrips	Sustained for 5 s	50	Requires patient cooperation

[a]Approximate percentage of receptors occupied when the response returns to its normal value.
Modified from Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonists. In Miller RD, ed. *Miller's Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone; 2005; and from Viby-Morgensen J, Claudius C. Neuromuscular monitoring. In Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier Saunders; 2015.

with an anticholinesterase drug (see Table 11.6) (see the section, "Antagonism of Nondepolarizing Neuromuscular Blocking Drugs").[24]

Tetanus

Tetanus (continuous or tetanic electrical stimulation for 5 seconds at about 50 Hz) is an intense stimulus for the release of ACh at the NMJ. In the presence of effects produced at the NMJ by nondepolarizing NMBDs, the response to tetanus is not sustained (fades), whereas in the presence of SCh-induced effects at the NMJ, the response to tetanus is greatly decreased but does not fade with a phase I blockade (see Fig. 11.10).[23] A sustained response to tetanus is present when the TOF ratio is greater than 0.7. At the cessation of tetanus, there is an increase in the immediately available stores of ACh such that the subsequent twitch responses are transiently enhanced (post-tetanic facilitation) (see Fig. 11.10).[23,25,26]

ANTAGONISM OF NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

For decades, antagonism of the effects of nondepolarizing NMBDs has been achieved by the intravenous administration of an anticholinesterase drug (usually neostigmine, but possibly and rarely edrophonium or pyridostigmine) on a routine basis. Now both neostigmine and sugammadex are available. Some principles are the same for both reversal drugs. Even if all tests of the adequacy of normal neuromuscular function are normal, 50% of the receptors at the NMJ may still be occupied by an NMBD. Patients will likely need more available receptors for adequate skeletal muscle strength. The unresolved question is if the response to peripheral nerve stimulation is normal, should one still give a small dose of neostigmine (e.g., 1.0 mg/70 kg) or sugammadex (e.g., 2 mg/kg)? An excellent rule to follow is, "When in doubt, it is better to have as many receptors free of the effects of NMBDs as possible" (see Tables 11.5 and 11.6).[23,24] Unequivocal clinical confirmation (sustained head lift or leg lift, or both, for 5 seconds, tongue depressor test, or a TOF > 0.9) provides assurance of adequate recovery (spontaneous and drug assisted) from the effects of NMBDs.

ADVERSE OUTCOMES FROM INADEQUATE ANTAGONISM OF NEUROMUSCULAR BLOCKADE

The time starting with the extubation of the trachea, transport to the PACU, and the first 30 minutes in the PACU can be one of the most dangerous times in the perioperative period. Inadequately antagonized or residual neuromuscular blockade can impair the integrity of the airway[28] and cause critical respiratory events in the PACU.[29] Analysis of large numbers of patients indicate that residual neuromuscular blockade is usually a component of adverse outcomes and even death. Specifically, residual neuromuscular blockade contributes to airway obstruction, inadequate ventilation, and hypoxia and has an incidence of 0.8% to 6.9%.[29] Other factors contributing to adverse effects in the PACU include obesity, opioids, emergency surgery, long duration of surgery, and abdominal surgery.[29] Clearly, clinicians should do everything possible to assure that residual neuromuscular blockade does not persist into the postoperative period by careful monitoring,[30,31] close observation, and alertness that such a blockade might exist.[32] The importance of residual neuromuscular blockade is increasingly recognized by scholarly analysis of this topic.[31-33]

Anticholinesterase Drugs (Neostigmine)

Anticholinesterase drugs are typically administered during the time when spontaneous recovery from the neuromuscular

blockade is occurring so that the effect of the pharmacologic antagonist adds to the rate of spontaneous recovery from the nondepolarizing NMBD. Neostigmine is the most common anticholinesterase drug currently used. The rapid spontaneous recovery rate characteristic of intermediate-acting NMBDs is an advantage over a long-acting NMBD such as pancuronium. For example, the incidence of weakness in the postoperative period despite administration of neostigmine is more frequent in patients receiving pancuronium than an intermediate- or short-acting NMBD.

Anticholinesterase drugs, such as neostigmine, accelerate the already established pattern of spontaneous recovery at the NMJ by inhibiting the activity of acetylcholinesterase and thereby leading to the accumulation of ACh at nicotinic neuromuscular and muscarinic sites. Increased amounts of ACh in the region of the NMJ improve the chance that two ACh molecules will bind to the α-subunits of the nicotinic cholinergic receptors (see Fig. 11.2). This action alters the balance of the competition between ACh and a nondepolarizing NMBD in favor of the neurotransmitter (ACh) and restores neuromuscular transmission. In addition, neostigmine may generate antidromic action potentials and repetitive firing of motor nerve endings (presynaptic effects).

The quaternary ammonium structure of anticholinesterase drugs greatly limits their entrance into the central nervous system such that selective antagonism of the peripheral nicotinic effects of nondepolarizing NMBDs at the NMJ is possible. For example, the peripheral cardiac muscarinic effects of neostigmine (bradycardia) are prevented by the prior or simultaneous intravenous administration of atropine or glycopyrrolate. In fact, either atropine or glycopyrrolate must be given when neostigmine is given.

Factors Influencing the Success of Antagonism of Neuromuscular Blocking Drugs

Factors influencing the success of antagonism of NMBDs include (1) the intensity of the neuromuscular blockade at the time that the pharmacologic antagonist is administered, (2) the choice of antagonist drug, (3) the dose of antagonist drug, (4) the rate of spontaneous recovery from the NMBD, and (5) the concentration of the inhaled anesthetic.

Although sugammadex is an exciting, relatively new antagonist of vecuronium and rocuronium, for over 50 years neostigmine has been the most commonly administered antagonist for nearly all nondepolarizing NMBDs. First, neostigmine will be described. The greater the spontaneous recovery, as judged by the response to peripheral nerve stimulation, the more rapidly complete recovery will occur from neostigmine administration. Although large doses of neostigmine will result in more rapid antagonism, the maximum dose should be limited to 60 to 70 μg/kg. Antagonism will be more rapid in the presence of an NMBD with rapid elimination (atracurium instead of pancuronium). The rate of antagonism can also be hastened by reducing the concentration of the volatile anesthetic.

Evaluation of the Adequacy of Antagonism

Adequacy of recovery (spontaneous and drug assisted) from the neuromuscular blocking effects produced by nondepolarizing NMBDs should be determined by the result of multiple tests of skeletal muscle strength (see Table 11.6).[30-33] Even though a TOF ratio of at least 0.9 has been recommended, visual estimation of the TOF is neither accurate nor reliable. In the absence of an accurately measured TOF ratio, a sustained response to tetanus or the ability to maintain head lift for 5 to 10 seconds usually indicates a TOF ratio greater than 0.9. Grip strength is also a useful indicator of recovery from the effects of NMBDs. Although a TOF ratio higher than 0.7 or its equivalent provides evidence of the patient's ability to sustain adequate ventilation, the pharyngeal musculature may still be weak and upper airway obstruction remains a risk. Furthermore, diplopia, dysphagia, an increased risk of aspiration of gastric contents, and a decreased ventilatory response to hypoxia in the presence of a TOF ratio more than 0.9 emphasize the value of more sensitive clinical methods for assessing neuromuscular function, such as sustained head lift or leg lift (or both) for 5 seconds or an evaluation of masseter muscle strength (tongue depressor test).[33]

Allowing spontaneous recovery from NMBDs without the aid of drug-assisted antagonism (i.e., administration of neostigmine or sugammadex) is not recommended unless there is compelling clinical evidence that significant residual neuromuscular blockade does not persist.

When the initial response to an anticholinesterase drug (i.e., neostigmine) seems inadequate, the following questions should be answered before additional antagonist drug is administered:

1. Has sufficient time elapsed for neostigmine or sugammadex to antagonize the nondepolarizing NMBD (15 to 30 minutes with neostigmine and more rapidly with sugammadex)?
2. Is the neuromuscular block too intense to be antagonized?
3. Is acid-base and electrolyte status normal?
4. Is body temperature normal?
5. Is the patient taking any drugs that could interfere with antagonism?
6. Has clearance of the nondepolarizing NMBD from plasma been decreased by renal or hepatic dysfunction (or by both)?

Answers to these questions will often provide the reason for failure of anticholinesterase drugs, such as neostigmine, to adequately antagonize nondepolarizing neuromuscular blockade.

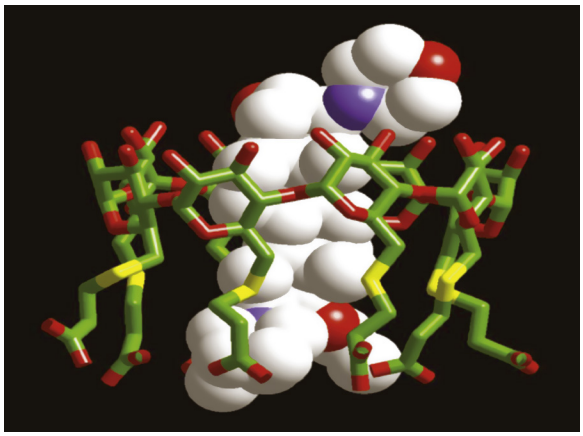

Fig. 11.11 The sugammadex-rocuronium complex. The white central structure is rocuronium. The green, red, and a bit of yellow tubular structure is sugammadex. A simple explanation is that sugammadex "encircles" rocuronium and transports it away from the neuromuscular junction. In the literature it is stated that sugammadex "encapsulates rocuronium." That complex leaves the neuromuscular junction to be excreted. The neuromuscular junction can then restore its normal function. (From Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed Engl.* 41:266-270, 2002.)

A New Antagonist of Neuromuscular Blocking Drugs[34]

A γ-cyclodextrin (sugammadex) (Fig. 11.11) is a relatively new antagonist, which antagonizes steroidal NMBDs, especially rocuronium and vecuronium, by encapsulating and inactivating them. Sugammadex transports rocuronium or vecuronium away from the NMJ. This mechanism of action is totally different from that of neostigmine in that no action on any cholinesterase takes place. Sugammadex has no action itself at the NMJ. The rate that it reliably reverses even a profound neuromuscular block is rapid (2 to 3 minutes) and complete. Furthermore, no cardiovascular effects occur; therefore, no other drug such as atropine is needed. Large doses of sugammadex can be given alone without cardiovascular effects. It could have significant impact in three major ways. First, a rocuronium-sugammadex combination can be used for a rapid sequence induction of anesthesia and recovery more rapid than with SCh. Second, it can allow more profound neuromuscular blocks to be induced intraoperatively without fear of inadequate reversal. Last, as indicated earlier, the incidence of residual neuromuscular blockade should be reduced or possibly eliminated.[35-37]

Sugammadex has been approved for use in Europe and successfully used in thousands of patients. It was approved in many other countries in 2010. As of December 2015, it has been approved in the United States. Many years ago, it was this author's original belief that sugammadex would completely replace neostigmine. Although sugammadex is growing in popularity, neostigmine is still commonly used as a routine antagonist of a rocuronium or possibly vecuronium neuromuscular blockade. Sugammadex has been much more expensive than neostigmine. Ironically, as reported in a "Letter to the Editor" in the August 2015 issue of the AANA, neostigmine may undergo additional review, which could alter its presentation and cost.

In certain clinical situations specific doses of sugammadex are recommended: (1) sugammadex, 2 mg/kg, if two of the four twitches from TOF stimulation appear; and (2) sugammadex, 4 mg/kg, should be given if one or two post-tetanic counts (PTC) occur and there is no recovery of the twitch response from TOF stimulation. These recommendations apply to either vecuronium or rocuronium. The last recommendation is for only rocuronium. If rocuronium, 1.2 mg/kg, has been given for a rapid sequence induction of anesthesia, the neuromuscular blockade can be terminated by giving sugammadex, 16 mg/kg. This approach may be necessary with extreme airway problems. Of prime importance is that nearly all of the FDA instructions or recommendations assume that adequate monitoring of neuromuscular function is being performed.

A common concept is to allow as much spontaneous recovery from neuromuscular blockade as possible before giving neostigmine. The ability of neostigmine to antagonize a profound neuromuscular blockade has always been questionable. Clearly the proper use of sugammadex should allow more clinical use of profound neuromuscular blockade and with a resultant successful reversal. One possibility is that laparoscopic surgery procedures may benefit from continuous profound neuromuscular blockade, especially when closing the surgical wound. Sugammadex can reverse a profound neuromuscular blockade.[37,38] Understandably, surgeons would prefer a profound neuromuscular block for the entire surgical procedure.[39] However, patient outcome is not clearly better. For example, Staehr-Rye and associates[38] found that deep neuromuscular blockade was only marginally better than moderate block for laparosopic cholecystectomy.

Anesthesia for electroconvulsive therapy is commonly achieved by the administration of thiopental and SCh. The use of rocuronium and sugammadex for electroconvulsive therapy may be associated with fewer cardiac arrhythmias and muscle pain.

SUMMARY

NMBDs are vital components of anesthetic care and airway management. When these drugs were introduced over 50 years ago, we were taught to either give small doses or even avoid paralysis if possible. We now have

much safer drugs, better antagonist drugs and monitoring devices, and more knowledge. We even have evidence that proper use of NMBDs can add a measure of safety if properly used.[33] The principles in this chapter represent contemporary use of NMBDs and their antagonists.[34]

QUESTIONS OF THE DAY

1. What is the normal sequence of neuromuscular transmission, beginning with the arrival of an impulse at the motor nerve terminal?
2. What mechanism is responsible for the termination of succinylcholine (SCh) neuromuscular blockade? How does this compare to the termination of acetylcholine's (ACh's) s actions at the neuromuscular junction?
3. What are the potential adverse effects of SCh? Which effects are potentially life threatening?
4. What are the train-of-four (TOF), double burst, and tetanus patterns of peripheral nerve stimulation? How can the results of peripheral nerve stimulation be used to determine if neuromuscular blockade is adequate for surgery?
5. How can TOF monitoring be used to determine whether a nondepolarizing neuromuscular block can be antagonized with neostigmine? How can the adequacy of antagonism be evaluated?
6. What is the mechanism of sugammadex antagonism of steroidal neuromuscular blockade? What are the clinical advantages and disadvantages of sugammadex compared to neostigmine?

REFERENCES

1. McNeill O, Kerridge RK, Boyle MJ. Review of procedures for investigation of anaesthesia-associated anaphylaxis in Newcastle, Australia. *Anaesth Intensive Care*. 2008;36:201–207.
2. Harboe T, Guttormsen AB, Irgens A, et al. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology*. 2005;102:897–903.
3. Gurrieri C, Weingarten TN, Martin DP. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg*. 2011;113:1202–1212.
4. Fagerlund MJ, Ericksson LI. Current concepts in neuromuscular transmission. *Br J Anaesth*. 2009;103:108–114.
5. Gronert GA. Succinylcholine-induced hyperkalemia and beyond. *Anesthesiology*. 1975;2009(111):1372–1377.
6. Martyn JAJ, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. *Anesthesiology*. 2006;104:158–169.
7. Miller R. Will succinylcholine ever disappear? *Anesth Analg*. 2004;98:1674–1675.
8. Naguib M, Lien CA, Aker J, et al. Posttetanic potentiation and fade in the response to tetanic and train-of-four stimulation during succinylcholine-induced block. *Anesth Analg*. 2004;98:1686–1691.
9. Baumann A, Studnicska D, Audibert G, et al. Refractory anaphylactic cardiac arrest after succinylcholine administration. *Anesth Analg*. 2009;109:137–140.
10. Holak EJ, Connelly JF, Pagel PS. Suxamethonium-induced hyperkalaemia 6 weeks after chemoradiotherapy in a patient with rectal carcinoma. *Br J Anaesth*. 2007;98:766–768.
11. Schreiber JU, Lysakowski C, Fuchs-Buder T, et al. Prevention of succinylcholine-induced fasciculation and myalgia: a meta-analysis of randomized trials. *Anesthesiology*. 2005;103:877–884.
12. Libonati MM, Leahy JJ, Ellison N. The use of succinylcholine in open eye surgery. *Anesthesiology*. 1985;62:637–640.
13. Kelly RE, Dinner M, Turner LS, et al. Succinylcholine increases intraocular pressure in the human eye with the extraocular muscles detached. *Anesthesiology*. 1993;79:948–952.
14. Farhan H, Moreno-Duarte I, Latronico N, et al. Acquired muscle weakness in the surgical intensive care unit: nosology, epidemiology, diagnosis, and prevention. *Anesthesiology*. 2016;124:207–234.
15. Appleton R, Kinsella J. Intensive care unit-acquired weakness. *Contin Educ Anaesth Crit Care Pain*. 2012;12:62–65.
16. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine and vecuronium for rapid sequence induction of anesthesia. *Anesthesiology*. 1993;79:913–918.
17. Sluga M, Ummenhofer W, Studer W, et al. Rocuronium versus succinylcholine for rapid sequence induction of anesthesia and endotracheal intubation: a prospective, randomized trial in emergent cases. *Anesth Analg*. 2005;101:1356–1361.
18. Mellinghoff H, Radbruch L, Diefenbach C, et al. A comparison of cisatracurium and atracurium: onset of neuromuscular block after bolus injection and recovery after subsequent infusion. *Anesth Analg*. 1996;83:1072–1075.
19. Brull SJ, Prielipp RC. Reversal of neuromuscular blockade. *Anesthesiology*. 2015;122:1183–1184.
20. McLean DJ, Diaz-Gil D, Farhan HN, et al. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *Anesthesiology*. 2015;122:1201–1216.
21. Ericksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. *Anesthesiology*. 2003;98:1037–1039.
22. Claudius C, Skovgaard LT, Viby-Mogensen J. Is the performance of acceleromyography improved with preload and normalization? *Anesthesiology*. 2009;110:1261–1270.
23. Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *Br J Anaesth*. 1982;54:209–223.
24. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology*. 1992;77:785–792.
25. Sayson SC, Mongan PD. Onset of action of mivacurium chloride: a comparison of neuromuscular blockade monitoring at the adductor pollicis and the orbicularis oculi. *Anesthesiology*. 1994;81:35–42.
26. Meistelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. *Can J Anaesth*. 1992;39:665–669.
27. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade to the clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology*. 1997;86:765–771.

28. Herbstreit F, Peters J, Eikermann M. Impaired upper airway integrity by residual neuromuscular blockade: increased airway collapsibility and blunted genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology*. 2009;110:1253–1260.
29. Murphy GS, Szokol JW, Marymont JH, et al. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg*. 2008;107:130–137.
30. Brull SJ, Naguib M, Miller RD. Residual neuromuscular block: rediscovering the obvious. *Anesth Analg*. 2008;107:11–14.
31. Murphy GS, Szokol JW, Marymont JH, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. *Anesthesiology*. 2008;109:389–398.
32. Kopman AF. Residual neuromuscular block and adverse respiratory events. *Anesth Analg*. 2008;107:1756.
33. Srivastava A, Hunter JM. Reversal of neuromuscular block. *Br J Anaesth*. 2009;103:115–129.
34. Caldwell JE, Miller RD. Clinical implications of sugammadex. *Anaesthesia*. 2009;64:66–72.
35. Hammaguchi S, Tezuka N, Nagao M. Rocuronium and sugammadex under TOF monitoring on mECT. *J Anesth*. 2015;29:815.
36. Bruekmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth*. 2015;115:743–751.
37. Kim HJ, Lee K, Park WK, et al. Deep neuromuscular block improves the surgical conditions for laryngeal microsurgery. *Br J Anaesth*. 2015;115:867–872.
38. Staehr-Rye AM, Rassmussen LS, Rosenberg J, et al. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade. *Anesth Analg*. 2014;119:1084–1091.
39. Donati F, Brull SJ. More muscle relaxation does not necessarily mean better surgeons or "the problem of muscle relaxation in surgery." *Anesth Analg*. 2014;119:1019–1021.