Chapter 13 – Pharmacology of Muscle Relaxants and Their Antagonists

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HISTORY AND CLINICAL USE

In 1942 Griffith and Johnson[1] suggested that *d*-tubocurarine (dTc) is a safe drug to use during surgery to provide skeletal muscle relaxation. One year later, Cullen[2] described its use in 131 patients who had received general anesthesia for their surgery. In 1954, Beecher and Todd[3] reported a sixfold increase in mortality in patients receiving dTc versus those who had not received a relaxant. The increased mortality was due to a general lack of understanding of the pharmacology of neuromuscular blockers and their antagonism. The impact of residual neuromuscular blockade postoperatively was not appreciated, guidelines for monitoring muscle strength had not been established, and the importance of pharmacologically antagonizing residual blockade was not understood. Since then, the understanding of neuromuscular blocker pharmacology has improved, and relaxants have become an important component of many anesthetics and have facilitated the growth of surgery into new areas with the use of innovative techniques.[4]

Succinylcholine, introduced by Thesleff[5] and by Foldes and colleagues in 1952,[4] changed anesthetic practice drastically. Its rapid onset of effect and ultrashort duration of action allowed for rapid tracheal intubation.

In 1967, Baird and Reid first reported on clinical administration of the synthetic aminosteroid pancuronium.[6] Though similar to dTc, in terms of its duration of action, this compound had an improved cardiovascular side effect profile. It lacked ganglionic-blocking and histamine-releasing properties and was mildly vagolytic. The resulting increases in heart rate and blood pressure were considered significant improvements over its predecessors. Unlike dTc or any of the nondepolarizing neuromuscular blockers previously used, none of which were metabolized, pancuronium underwent some hepatic metabolism through deacetylation of the acetoxy groups.

Development of the intermediate-acting neuromuscular blockers built on compound metabolism and resulted in the introduction of vecuronium,[7] an aminosteroid, and atracurium,[8][9] a benzylisoquinolinium, into practice in the 1980s. These relaxants had little or no dependence on the kidney for elimination. The lack of cardiovascular effects of vecuronium established a benchmark for safety to which newer relaxants are still held.[7] Degradation of atracurium by Hofmann elimination removed any important influence of biologic disorders such as advanced age or organ failure on the pattern of neuromuscular blockade.

Mivacurium, the first short-acting nondepolarizing neuromuscular blocker, was introduced into clinical practice in the 1990s,[10] as was rocuronium,[11] an intermediate-acting nondepolarizing blocker with a rapid onset of effect. Mivacurium, like the intermediate-acting compounds, is extensively metabolized. It is, however, metabolized by butyrylcholinesterase, the same enzyme that is responsible for the metabolism of succinylcholine. In terms of facilitating rapid endotracheal intubation, rocuronium is the

first nondepolarizing neuromuscular blocker considered to be a replacement for succinylcholine.

Other neuromuscular blockers have been introduced into clinical practice since the use of dTc was first advocated. These blockers include pipecuronium, doxacurium, cisatracurium, and rapacuronium. Although all do not remain in use, each represented an advance or improvement in at least one aspect over its predecessors. Still other neuromuscular blockers, TAAC3[12] and 430A,[13] are undergoing investigation.

Neuromuscular blockers should be administered only to anesthetized individuals to provide relaxation of skeletal muscles. They should not be administered to stop patient movement because they have no analgesic or amnestic properties. Awareness during surgery[14] and in the intensive care unit (ICU)[15] has been described in multiple publications. Neuromuscular blockers are valuable adjuncts to general anesthetics and should be used as such. As stated by Cullen and Larson, "muscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in ... a patient [who] is paralyzed but not anesthetized—a state that [is] wholly unacceptable for the patient."[16] Additionally, "muscle relaxants used to cover up deficiencies in total anesthetic management ... represent an ... inappropriate use of the valuable adjuncts to anesthesia." To administer relaxants for maintenance of neuromuscular blockade intraoperatively, the patient's depth of neuromuscular block must be monitored and the depth of anesthesia continuously assessed.

The use of neuromuscular blockers in the operating room is quite common and has been important in the growth and development of anesthesia and surgery. As stated by Foldes and coauthors,[4] "... [the] first use of ... muscle relaxants ... not only revolutionized the practice of anesthesia but also started the modern era of surgery and made possible the explosive development of cardiothoracic, neurologic and organ transplant surgery." Certainly, neuromuscular blockers are now routinely used to facilitate endotracheal intubation and are commonly used to maintain neuromuscular blockade through any number of different surgical procedures. This chapter will review the pharmacology and clinical use of neuromuscular blockers, as well as anticholinesterases, in the operating room. Diseases of the neuromuscular system are also discussed as regards their influence on the actions of neuromuscular blockers. Finally, the economics of providing neuromuscular blockade is also considered.

PRINCIPLES OF ACTION OF NEUROMUSCULAR BLOCKERS AT THE NEUROMUSCULAR JUNCTION (also see Chapter 22)

Postjunctional Effects

In adult mammalian skeletal muscle, the nicotinic acetylcholine receptor (nAChR) is a pentameric complex of two α-subunits in association with single β-, δ-, and ϵ-subunits (Fig. 13-1). These subunits are organized to form a transmembrane pore (a channel), as well as the extracellular binding pockets for acetylcholine and other agonists or antagonists.[17] Each of the two α-subunits has an acetylcholine-binding site. These sites are proteins located in pockets approximately 3.0 nm above the surface membrane at the interfaces of the α_H-ϵ and α_L-δ subunits.[18] α_H and α_L indicate the high- and low-affinity binding sites for dTc and probably result from a contribution from the different

neighboring subunits.[19][20] For instance, the binding affinity of dTc for the α_H-ϵ site is approximately 100- to 500-fold higher than that for the α_L-δ site.[18][20][21] Fetal nAChR contains a γ-subunit instead of the adult ϵ-subunit. Mature nAChR has a shorter burst duration and exhibits higher conductance of Na^+, K^+, and Ca^{2+} than fetal nAChR does.[17][22]

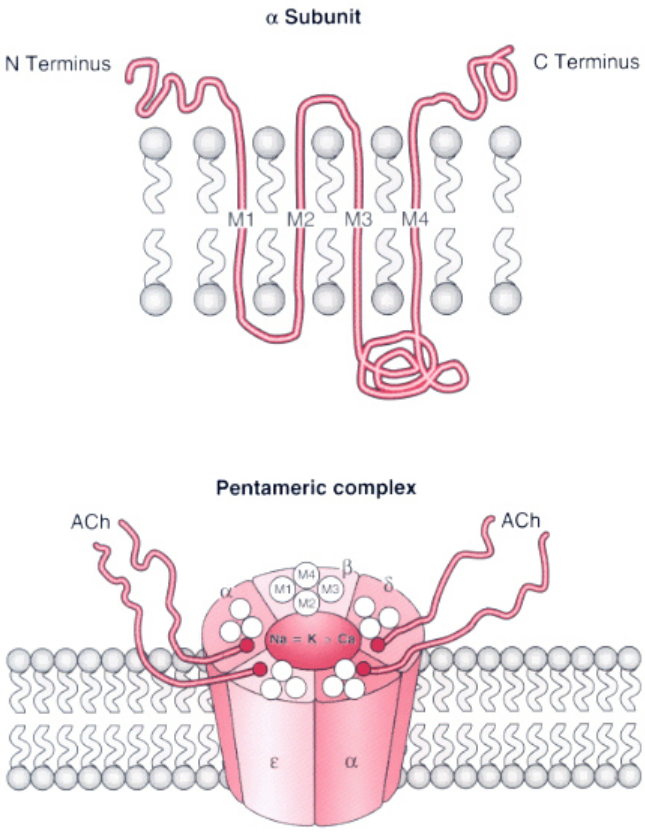

Figure 13-1 Subunit composition of the nicotinic acetylcholine receptor (nAChR) in the end-plate surface of adult mammalian muscle. The adult AChR is an intrinsic membrane protein with five distinct subunits (α_2βδϵ). Each subunit contains four helical domains labeled M1 to M4. The M2 domain forms the channel pore. The *upper panel* shows a single α-subunit with its N and C termini on the extracellular surface of the membrane lipid bilayer. Between the N and C termini, the α-subunit forms four helices (M1, M2, M3, and M4) that span the membrane bilayer. The *lower panel* shows the pentameric structure of the nAChR of adult mammalian muscle. The N termini of two subunits cooperate to form two distinct binding pockets for acetylcholine (ACh). These pockets occur at the ϵ-α and the δ-α subunit interface. The M2 membrane-spanning domain of each subunit lines the ion channel. The doubly liganded ion channel has permeability equal to that of Na^+ and K^+; Ca^{2+} contributes approximately 2.5% to the total permeability.
(Redrawn from Naguib M, Flood P, McArdle JJ, et al: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. Anesthesiology 96:202–231, 2002.)

Functionally, the ion channel of the acetylcholine receptor is closed in the resting state. Simultaneous binding of two acetylcholine molecules to the α-subunits[23] initiates conformational changes that open the channel.[24][25][26] On the other hand, it is enough for one molecule of a nondepolarizing neuromuscular blocker (a competitive antagonist) to bind to one subunit to produce a block.[27] Paul and coworkers[28] found a correlation

between the ED_{50} (the dose that produces 50% depression of twitch tension) and the potency of nondepolarizing blockers at the adult nAChR.

Depolarizing neuromuscular blockers such as succinylcholine produce prolonged depolarization of the end-plate region that results in (1) desensitization of nAChR, (2) inactivation of voltage-gated sodium channels at the neuromuscular junction, and (3) increases in potassium permeability in the surrounding membrane (see Chapter 22 for details).[27] The end result is failure of action potential generation, and block ensues. It should be noted that although acetylcholine produces depolarization, under physiologic conditions it results in muscle contraction because it has a very short (few milliseconds) duration of action.[27] Acetylcholine is rapidly hydrolyzed by acetylcholinesterase[29] to acetic acid and choline. Administration of large doses of acetylcholine in experimental animals, though, produces neuromuscular blockade.[27]

The fetal nAChR is a low-conductance channel, in contrast to the high-conductance channel of adult nAChR. Thus, acetylcholine release causes brief activation and a reduced probability of channel opening.[17] The upregulation of nAChRs that is found in states of functional or surgical denervation is characterized by the spreading of predominantly fetal-type nAChRs. These receptors are resistant to nondepolarizing neuromuscular blockers and more sensitive to succinylcholine.[30] When depolarized, the immature isoform has a prolonged open channel time, which exaggerates K^+ efflux.[31]

Prejunctional Effects

Prejunctional receptors are involved in the modulation of acetylcholine release in the neuromuscular junction. The existence of both nicotinic and muscarinic receptors on motor nerve endings has been described. The prejunctional nicotinic receptor is a pentameric complex composed of $\alpha_3\beta_2$-subunits. Bowman[32] suggested that the prejunctional nicotinic receptors are activated by acetylcholine and function in a positive-feedback control system that serves to maintain the availability of acetylcholine when demand for it is high (e.g., during tetany).[32] Blockage of these receptors by nondepolarizing neuromuscular blockers would explain the fade phenomenon seen with tetanic and train-of-four (TOF) stimulation.[32][33] The G protein-coupled muscarinic receptors are also involved in the feedback modulation of acetylcholine release.[34][35][36] The prejunctional M_1 and M_2 receptors are involved in facilitation and inhibition of acetylcholine release, respectively, through modulation of Ca^{2+} influx,[37][38] whereas the prejunctional nicotinic receptors are involved in mobilization of acetylcholine, but not in the release process directly.[39] Hence, blockade of prejunctional nicotinic receptors by nondepolarizing neuromuscular blockers prevents acetylcholine from being made available fast enough to support tetanic or TOF stimulation. In contrast, prejunctional muscarinic receptors are involved in upmodulation or downmodulation of the release mechanism. No evidence has indicated that nondepolarizing neuromuscular blockers act on muscarinic receptors.

MONITORING NEUROMUSCULAR FUNCTION

Details of monitoring neuromuscular function are discussed in Chapter 39. In this section, general concepts of monitoring as they relate to the clinical use of neuromuscular blockers are presented.

Peripheral Nerve Stimulation and Clinical Tests

Monitoring of neuromuscular function after the administration of neuromuscular blocking agents is extremely important to appropriately dose these agents and to better guarantee patient safety.[40][41] In the operating room or the ICU, the depth of neuromuscular blockade is typically monitored by observing the response of any superficially located neuromuscular unit to stimulation. Most commonly, contraction of the adductor pollicis associated with stimulation of the ulnar nerve, either at the wrist or at the elbow, is monitored. In certain circumstances, depending on patient positioning where access to the patient's arms may be limited or because of the nature of the injury, the peroneal nerve or the facial nerve may be monitored.

The pattern of response to TOF stimulation (four stimuli delivered over a period of 2 seconds) or a tetanic stimulus varies with the type of neuromuscular blocker administered because the two relaxant types, depolarizing and nondepolarizing, have different mechanisms of action. With a complete block, no response to either mode of stimulation should be seen. However, during partial neuromuscular blockade, different responses are seen to these modes of stimulation, depending on the agent administered. Nondepolarizing neuromuscular blocking agents are competitive inhibitors of the acetylcholine receptor—they compete with acetylcholine for the active, or binding, sites on the α-subunits of the receptor. With repetitive or intense stimulation, the response to stimulation fades over time because of a decrease in the amount of acetylcholine released from the prejunctional nerve terminal with successive stimuli. The fourth response to a TOF stimulus is decreased relative to the first response (Fig. 13-2) because the lesser amount of acetylcholine released into the synaptic cleft with the fourth stimulus cannot overcome the competitive block as readily. Similarly, fade is seen in the response to tetanic stimuli when a partial nondepolarizing neuromuscular block is present. During neuromuscular blockade with nondepolarizing agents, if one administers a TOF stimulus shortly after administering a tetanic stimulus, the response to stimulation is augmented and neuromuscular function appears stronger than it did just a couple of minutes earlier. This presumably occurs because with the tetanic stimuli, acetylcholine is mobilized toward the presynaptic portion of the nerve terminal and then, with subsequent stimulation (TOF), an increased amount of acetylcholine is released into the synaptic cleft and the block imposed by the nondepolarizing agent is more readily overcome. It may take from 1 to 10 minutes for recovery to return to pretetanic or baseline values.[42][43] In the case of administration of a depolarizing neuromuscular blocking agent such as succinylcholine, the response that has been classically described is quite different. With repetitive TOF stimuli, after the administration of doses of succinylcholine that cause 100% paralysis, four equal responses are seen with each stimulus, but the response weakens with each successive TOF stimulus (Fig. 13-3). Similarly, no fade or weakening in the response to a tetanic stimulus takes place; however, the entire response will be weaker than it was at baseline. The onset of

blockade after the administration of small doses of succinylcholine, 0.05 to 0.3 mg/kg, is accompanied by fade in the TOF response, as has been described for nondepolarizing agents.[44] Interestingly, although one would not necessarily anticipate that there would be posttetanic potentiation after the administration of succinylcholine, it has been described.[45] The reason for this observation has yet to be elucidated.

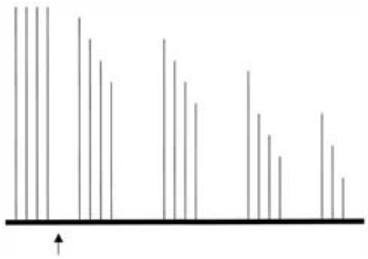

Figure 13-2 Schematic representation of the onset of a neuromuscular block after administration of a nondepolarizing neuromuscular blocking agent at the *arrow*. Neuromuscular function is monitored with repetitive train-of-four (TOF) stimuli (four stimuli of 0.5-msec duration administered over a period of 2 seconds). Note the presence of fade in the response to TOF stimulation.

Figure 13-3 Schematic representation of the onset of a neuromuscular block after administration of a depolarizing neuromuscular blocking agent at the *arrow*. Neuromuscular function is monitored with repetitive train-of-four stimuli (four stimuli of 0.5-msec duration administered over a period of 2 seconds).

Donati and colleagues[46] and Pansard and associates[47] have demonstrated that neuromuscular blockade develops faster in centrally located muscles, such as the larynx, the jaw, and the diaphragm, than in more peripherally located muscles, such as the adductor pollicis. In addition to developing more quickly, neuromuscular blockade in these regions, at a given dose, is less profound and recovers more quickly (Fig. 13-4) (for details see the section "Neuromuscular Blockers and Tracheal Intubation").[46] Consequently, the choice of monitoring site is important.

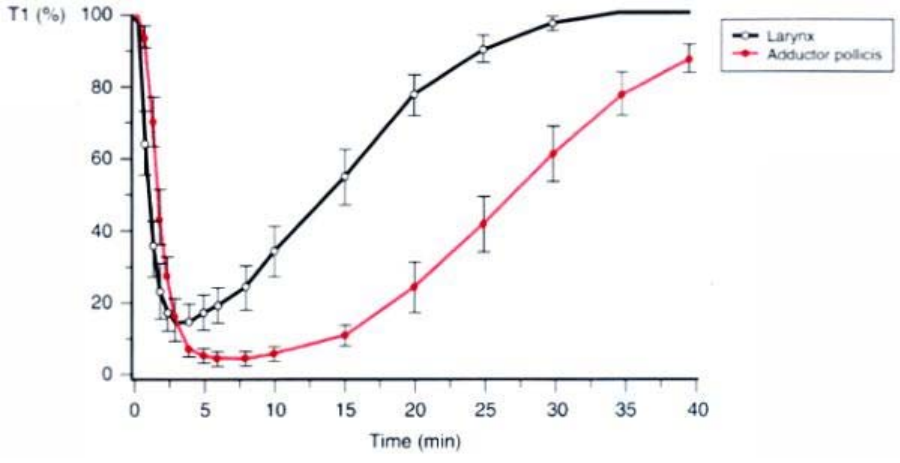

Figure 13-4 Evolution of neuromuscular blockade in the larynx and thumb (adductor pollicis) after 0.07 mg/kg vecuronium. Onset and recovery from the block occur more rapidly in the larynx.

(Redrawn from Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. Anesthesiology 74:833–837, 1991.)

To determine the depth of block during maintenance and recovery of neuromuscular function, the response of the adductor pollicis to stimulation of the ulnar nerve should be monitored. If recovery in this neuromuscular unit is complete, recovery in the musculature of the airway should also be complete.[46]

Peripheral nerve stimulation can be used to determine both the magnitude and the depth of neuromuscular blockade. However, the degree of neuromuscular block must be assessed cautiously. Because there is such a wide margin of safety as regards neuromuscular function, with a large number of acetylcholine receptors having to be blocked before weakness becomes detectable, the reduction in contractile response to peripheral nerve stimulation is not proportional to the action of neuromuscular blockers at the receptor. Waud and Waud[48] demonstrated that the twitch response of the tibialis anterior muscle of the cat in response to a single supramaximal stimulus is not reduced unless more than 70% of the receptors are occupied by a nondepolarizing neuromuscular blocker. Twitch is completely eliminated when 90% of the receptors are occupied. Three questions can be answered by observing the response to peripheral nerve stimulation: (1) is the neuromuscular blockade adequate? (2) is the neuromuscular blockade excessive? and (3) can the neuromuscular blockade be antagonized?

Muscle contraction is an all-or-none phenomenon. Each fiber either contracts maximally or does not contract at all. Therefore, when twitch height, or muscle strength, is reduced, some fibers are contracting normally and others are blocked and remain flaccid. A stronger response indicates that fewer muscle fibers remain flaccid.

Because the interaction of nondepolarizing neuromuscular blockers with acetylcholine receptor binding sites is competitive, neuromuscular blockade can be overcome by increasing—or intensified by reducing—the concentration of acetylcholine. This concept is important in clinical monitoring of neuromuscular blockade. Another important concept is the economy of acetylcholine synthesis, storage, and release. The quantity of acetylcholine released with each nerve action potential is inversely proportional to the number of action potentials reaching the nerve terminal per unit time, or the stimulus frequency. The depth of blockade of evoked neuromuscular responses in the presence of nondepolarizing neuromuscular blockers is directly proportional to the stimulus frequency.

The onset of neuromuscular blockade should be monitored with either single twitch stimuli or TOF stimuli because one is looking for ablation of the twitch response, or its maximal suppression, to determine onset of the block. The depth of block during maintenance of blockade and recovery should be monitored with repeated TOF stimuli, where depending on the surgery and the type of anesthetic administered, the anesthesiologist may want to maintain deeper levels of neuromuscular blockade (one or two twitches in response to TOF stimuli) or lesser degrees of blockade (three to four twitches in response to TOF stimuli).

When determining the depth of block to maintain during the course of an anesthetic, it is important to remember that a deep volatile anesthetic will provide some degree of muscle relaxation and patient immobility and that volatile anesthetics potentiate nondepolarizing neuromuscular blockers. Similarly, recovery of neuromuscular function should be monitored with TOF stimuli. Once four responses to stimulation are detectable and fade in the response is no longer detectable, the TOF ratio (the strength of the fourth response in comparison to the strength of the first response to stimulation) may be 40% to 100%. It is difficult to more reliably detect fade in the TOF response[48][49] because the middle two responses confuse interpretation of the first and fourth responses. Once fade in response to TOF stimulation is no longer detected, adequacy of recovery should be confirmed with double-burst stimulation. In response to this stimulus, the clinician feels only two responses,[50] thus simplifying interpretation of the relative strength of each response. If no difference in the two responses is apparent, the TOF ratio is at least 0.6.[51][52]

In addition to using monitors of muscle strength, clinical indicators of adequacy of return of neuromuscular function should also be sought. Such clinical tests include a 5-second head lift, handgrip, and in a patient unable to cooperate with simple commands, the ability to bend the legs up off the operating room table. A successful head lift is one done from a flat surface, unaided and maintained for a full 5 seconds. Pavlin and coworkers[53] have shown that if patients can successfully perform a head lift, their maximum inspiratory force is approximately -55 cm H_2O, and if they can lift their legs off a flat surface, their maximum inspiratory force is -50 cm H_2O. With a strong handgrip, clinicians should not be able to pull their fingers from the patient's grip. Even though these tests have long been the mainstay of clinical tests of neuromuscular function, they can be accomplished over a wide range of TOF ratios and must be used with caution. As described by Kopman and coauthors,[54] volunteers with TOF ratios as low as 0.5 are capable of maintaining a 5-second head lift and having a strong handgrip. The ability of patients to oppose their incisors and maintain a tongue blade between them appears to be a more sensitive indicator of the adequacy of muscle strength inasmuch as volunteers were unable to perform this task until their TOF ratios had returned to 0.85. In patients, however, even this ability does not seem to be a sensitive indicator of residual neuromuscular block.[55]

Monitors of respiratory function do not reliably indicate return of muscle strength and function to baseline. Tidal volume is inadequate as a monitor of the adequacy of muscle strength because it is more likely to reflect recovery in the centrally located muscles of respiration and is dependent on diaphragmatic movement only. With a tidal volume of at least 5 mL/kg, 80% of acetylcholine receptors may still be occupied by nondepolarizing neuromuscular blocking drugs. Head lift and handgrip may be 38% and 48% of control, respectively, when both inspiratory and expiratory flow rates are more than 90% of control.[56] Furthermore, inspiratory force may be only 70% of control when vital capacity and the expiratory flow rate are greater than 90% of control values.[57]

Clinical Applications

It is not known what proportion of receptors must be available or how sensitive a test must be to ensure adequate muscle strength to overcome airway obstruction and permit effective coughing and to be free of visual disturbances. The anesthesiologist should not rely on just

one test of neuromuscular strength, but should use as many tests as practically possible (Table 13-1). The results of Pavlin and colleagues[53] and the relatively frequent admission of patients to the postanesthesia care unit (PACU) with unacceptable levels of neuromuscular blockade that was unrecognized by the anesthesiologist[58][59][60] emphasize the difficulty in ensuring that no residual neuromuscular blockade exists after surgery and anesthesia.

Table 13-1 -- Tests of neuromuscular transmission

	Acceptable Clinical Results to Suggest Normal Function	Approximate Percentage of Receptor Occupied When Response Returns to Normal Value	Comments/Disadvantages/Advantages
Tidal volume	At least 5 mL/kg	80	Insensitive as an indicator of peripheral neuromuscular function
Single twitch	Qualitatively as strong as baseline	75–80	Uncomfortable, need to know twitch strength before relaxant strength as baseline administration. Insensitive as an indicator of recovery, but useful as a gauge of deep neuromuscular blockade
Train-of-four (TOF)	No palpable fade	70–75	Still uncomfortable, but more sensitive as an indicator of recovery than single twitch is. Useful as a gauge of depth of block by counting the number of responses perceptible
Sustained tetanus at 50 Hz for 5 sec	No palpable fade	70	Very uncomfortable, but a reliable indicator of adequate recovery
Vital capacity	At least 20 mL/kg	70	Requires patient cooperation, but is the goal for achievement of full clinical recovery
Double burst	No palpable fade	60–70	Uncomfortable, but more sensitive than TOF as an indicator of stimulation of peripheral function. No perceptible fade indicates TOF recovery of at least 60%
Sustained tetanus at 100 Hz	No palpable fade	50	Very painful, a "stress test" for the neuromuscular junction. It is not always possible to achieve or demonstrate lack of fade at 100 Hz
Inspiratory force	At least -40 cm H_2O	50	Sometimes difficult to perform without endotracheal intubation, but a reliable gauge of

	Acceptable Clinical Results to Suggest Normal Function	Approximate Percentage of Receptor Occupied When Response Returns to Normal Value	Comments/Disadvantages/Advantages
			normal diaphragmatic function
Head lift	Must be performed unaided with patient supine at 180 degrees and for 5 sec	50	Requires patient cooperation, but remains the standard test of normal clinical function. Must be performed with the patient in a completely supine position
Handgrip	Sustained at a level qualitatively similar to preinduction baseline	50	Sustained strong grip, though also requiring patient cooperation. It is another good gauge of normal function
Sustained bite	Sustained jaw clench on tongue blade	50	Very reliable with patient cooperation. Corresponds to TOF ratio of 0.85

PHARMACOLOGY OF SUCCINYLCHOLINE

Structure-Activity Relationships

All neuromuscular blockers are structurally related to acetylcholine. Neuromuscular blocking agents are quaternary ammonium compounds. Positive charges at these sites in the molecules mimic the quaternary nitrogen atom of the transmitter acetylcholine and are the principal reason for the attraction of these drugs to cholinergic nicotinic receptors at the neuromuscular junction. These receptors are also located at other physiologic sites of acetylcholine in the body, such as the nicotinic receptors in autonomic ganglia and as many as five different muscarinic receptors on both the parasympathetic and sympathetic sides of the autonomic nervous system. In addition, populations of nicotinic and muscarinic receptors are located prejunctionally at the neuromuscular junction.[27]

The depolarizing neuromuscular blocker succinylcholine is composed of two molecules of acetylcholine linked back to back through the acetate methyl groups (Fig. 13-5). As described by Bovet,[61] succinylcholine is a long, thin, flexible molecule. Like acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and at nicotinic (ganglionic) and muscarinic autonomic sites to open the ionic channel in the acetylcholine receptor.

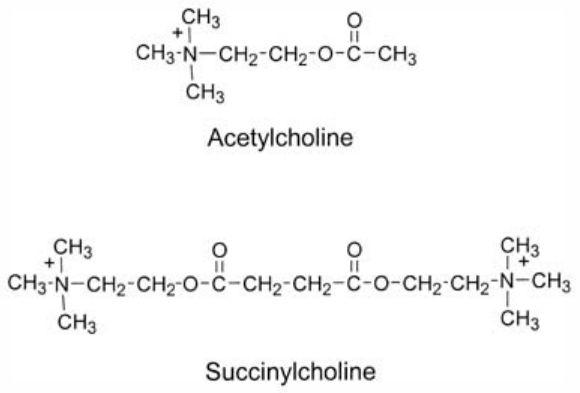

Figure 13-5 Structural relationship of succinylcholine, a depolarizing neuromuscular blocking agent, to acetylcholine. Succinylcholine consists of two acetylcholine molecules linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates nicotinic receptors at the neuromuscular junction.

Pharmacokinetics and Pharmacodynamics

Succinylcholine is the only available neuromuscular blocker with a rapid onset of effect and an ultrashort duration of action. The ED_{95} of succinylcholine (the dose causing on average 95% suppression of neuromuscular response) is 0.51 to 0.63 mg/kg.[62][63] Using cumulative dose-response techniques, Smith and coworkers[64] and Kopman and associates[65] have estimated that its potency is far greater with an ED_{95} less than 0.3 mg/kg.

Administration of 1 mg/kg succinylcholine results in complete suppression of response to neuromuscular stimulation in approximately 60 seconds.[66][67][68] In patients with genotypically normal butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase) activity, recovery to 90% muscle strength after the administration of 1 mg/kg succinylcholine requires from 9 to 13 minutes.[69][70]

The short duration of action of succinylcholine is due to its rapid hydrolysis by butyrylcholinesterase to succinylmonocholine and choline. Butyrylcholinesterase has an enormous capacity to hydrolyze succinylcholine, and only 10% of the administered drug reaches the neuromuscular junction.[71] The initial metabolite (succinylmonocholine) is a much weaker neuromuscular blocking agent than succinylcholine is[72] and is metabolized much more slowly to succinic acid and choline. In dogs,[73] after the administration of 0.5 and 1.0 mg/kg, its $t_{½}\beta$ is 5 minutes. Its $t_{½}\alpha$ is less than 1 minute.[69]

Because little or no butyrylcholinesterase is present at the neuromuscular junction, the neuromuscular block induced by succinylcholine is terminated by its diffusion away from the neuromuscular junction back into the circulation. Butyrylcholinesterase therefore influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed before it reaches and after it leaves the neuromuscular junction.

Dibucaine Number and Butyrylcholinesterase Activity

Butyrylcholinesterase is synthesized by the liver and is found in plasma. The neuromuscular block induced by succinylcholine is prolonged by a decreased concentration or activity of the enzyme. The activity of the enzyme refers to the number of substrate molecules (µmol) hydrolyzed per unit of time, often expressed in international units (IU). The normal range of butyrylcholinesterase activity is quite large, and as demonstrated by Viby-Mogensen,[69]

significant decreases in butyrylcholinesterase activity result in modest increases in the time required to achieve 100% twitch recovery (Fig. 13-6).

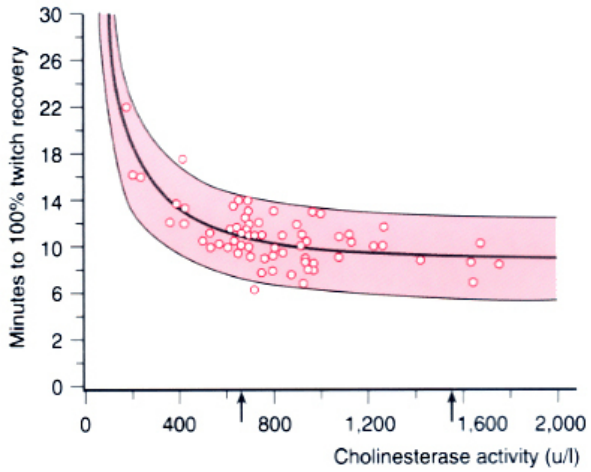

Figure 13-6 Correlation between the duration of succinylcholine neuromuscular blockade and butyrylcholinesterase activity. The normal range of activity lies between the *arrows*.
(From Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme. Anesthesiology 53:517–520, 1980.)

Factors that have been found to lower butyrylcholinesterase activity are liver disease,[74] advanced age,[75] malnutrition, pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, anticholinesterase drugs,[76][77] tetrahydroaminacrine,[78] hexafluorenium,[79][80] and metoclopramide.[81] The histamine type 2 (H_2) receptor antagonists have no effect on butyrylcholinesterase activity or the duration of succinylcholine effect.[82] Bambuterol, a prodrug of terbutaline, produces marked inhibition of butyrylcholinesterase activity and causes prolongation of succinylcholine-induced blockade.[83][84] The β-blocker esmolol inhibits butyrylcholinesterase but causes only minor prolongation of succinylcholine blockade.[85][86]

Despite all the publications and efforts to identify situations in which normal butyrylcholinesterase enzyme activity may be low, this has not been a major concern in clinical practice because even large decreases in butyrylcholinesterase activity result in only moderate increases in the duration of action of succinylcholine. When butyrylcholinesterase activity is reduced to 20% of normal by severe liver disease, the duration of apnea after the administration of succinylcholine increases from a normal duration of 3 minutes to only 9 minutes. Even when glaucoma treatment with echothiophate decreased butyrylcholinesterase activity from 49% of control to no activity, the increase in duration of neuromuscular blockade varied from 2 to 14 minutes. In no patient did the total duration of neuromuscular blockade exceed 23 minutes.[87]

Dibucaine Number and Atypical Butyrylcholinesterase

Succinylcholine-induced neuromuscular blockade can be significantly prolonged if the patient has an abnormal genetic variant of butyrylcholinesterase. The variant was found by Kalow and Genest[88] to respond to dibucaine differently than normal butyrylcholinesterase does. Dibucaine inhibits normal butyrylcholinesterase to a far greater extent than it does the abnormal enzyme. This observation led to development of the test for dibucaine number. Under standardized test conditions, dibucaine inhibits the normal enzyme about 80% and the abnormal enzyme about 20% (Table 13-2). Subsequently, many other genetic variants of butyrylcholinesterase have been identified, although dibucaine-resistant variants are the most important. Reviews by Pantuck[89] and by Jensen and Viby-Mogensen[90] can be consulted for more detailed information on this topic.

Table 13-2 -- Relationship between dibucaine number and duration of succinylcholine or mivacurium neuromuscular blockade

Type of Butyrylcholinesterase	Genotype	Incidence	Dibucaine Number*	Response to Succinylcholine or Mivacurium
Homozygous typical	UU	Normal	70–80	Normal
Heterozygous atypical	UA	1/480	50–60	Lengthened by about 50%–100%
Homozygous atypical	AA	1/3200	20–30	Prolonged to 4–8 hr

* The dibucaine number indicates the percentage of enzyme inhibited.

Although the dibucaine number indicates the genetic makeup of an individual with respect to butyrylcholinesterase, it does not measure the concentration of the enzyme in plasma, nor does it indicate the efficiency of the enzyme in hydrolyzing a substrate such as succinylcholine or mivacurium. Both the latter factors are determined by measuring butyrylcholinesterase activity—which may be influenced by genotype.

The molecular biology of butyrylcholinesterase is well understood. The amino acid sequence of the enzyme is known, and the coding errors responsible for most genetic variations have been identified.[89][90] Most variants are due to a single amino acid substitution error or sequencing error at or near the active site of the enzyme. For example, in the case of the "atypical" dibucaine-resistant (A) gene, a mutation occurs at nucleotide 209, where guanine is substituted for adenine. The resultant change in this codon causes substitution of glycine for aspartic acid at position 70 in the enzyme. In the case of the fluoride-resistant (F) gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243 and valine for glycine at position 390. Table 13-2 summarizes many of the known genetic variants of butyrylcholinesterase: the amino acid substitution at position 70 is written as Asp Ø Gly. New variants of butyrylcholinesterase genotypes continue to be discovered.[91][92]

Side Effects

Cardiovascular Effects

Succinylcholine-induced cardiac dysrhythmias are many and varied. The drug stimulates all cholinergic autonomic receptors: nicotinic receptors on both sympathetic and parasympathetic ganglia[93] and muscarinic receptors in the sinus node of the heart. In low doses, both negative inotropic and chronotropic responses may occur. These responses can be attenuated by previous administration of atropine. With large doses of succinylcholine, these effects may become positive[94] and tachycardia ensues. A prominent clinical manifestation of generalized autonomic stimulation is the development of cardiac dysrhythmias, principally sinus bradycardia, junctional rhythms, and ventricular dysrhythmias. Clinical studies have described these dysrhythmias under various conditions in the presence of the intense autonomic stimulus of tracheal intubation. It is not entirely clear whether the cardiac irregularities are due to the action of succinylcholine alone or due to the added presence of extraneous autonomic stimulation.

Sinus Bradycardia

The autonomic mechanism involved in sinus bradycardia is stimulation of cardiac muscarinic receptors in the sinus node, which is particularly problematic in individuals with predominantly vagal tone, such as children who have not received atropine.[95][96] Sinus bradycardia has also been noted in adults and appears more commonly when a second dose of the drug is given approximately 5 minutes after the first.[97] The bradycardia may be prevented by thiopental,[98][99] atropine,[98] ganglion-blocking drugs, and nondepolarizing neuromuscular blockers.[98][100] The implication from this information is that direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in the bradycardiac response. The higher incidence of bradycardia after a second dose of succinylcholine[100] suggests that the hydrolysis products of succinylcholine (succinylmonocholine and choline) may sensitize the heart to a subsequent dose.

Nodal (Junctional) Rhythms

Nodal rhythms commonly occur after the administration of succinylcholine. The mechanism probably involves relatively greater stimulation of muscarinic receptors in the sinus node and, as a result, suppression of the sinus mechanism and emergence of the atrioventricular node as the pacemaker. The incidence of junctional rhythm is greater after a second dose of succinylcholine but is prevented by previous administration of dTc.[98][100]

Ventricular Dysrhythmias

Under stable anesthetic conditions, succinylcholine lowers the threshold of the ventricle to catecholamine-induced dysrhythmias in the monkey and dog. Circulating catecholamine concentrations increase fourfold and potassium concentrations increase by a third after succinylcholine administration in dogs.[101] Similar increases in catecholamine levels are also observed after the administration of succinylcholine to humans.[102][103] Other autonomic stimuli, such as endotracheal intubation,[104] hypoxia, hypercapnia, and surgery, may be additive to the effect of succinylcholine. The possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine oxidase inhibitors, exogenous catecholamines, and halothane, all of which may lower the ventricular threshold for ectopic activity or increase the arrhythmogenic effect of catecholamines, must be considered as well. Ventricular escape beats may also occur as a result of severe sinus and atrioventricular

nodal slowing secondary to succinylcholine administration. The development of ventricular dysrhythmias is further encouraged by the release of potassium from skeletal muscle as a consequence of the depolarizing action of the drug.

Hyperkalemia

The administration of succinylcholine to an otherwise well individual for an elective surgical procedure increases plasma potassium levels by approximately 0.5 mEq/L. This increase in potassium is due to the depolarizing action of the relaxant. With activation of the acetylcholine channels, movement of sodium into the cells is accompanied by movement of potassium out of the cells. This slight increase in plasma potassium levels is well tolerated by individuals and generally does not cause dysrhythmias.

Several early reports suggested that patients in renal failure may be susceptible to a hyperkalemic response to succinylcholine.[105][106][107] Nevertheless, more controlled studies have shown that renal failure patients are no more susceptible to an exaggerated response to succinylcholine than are those with normal renal function.[108][109][110][111][112] One might postulate that patients who have uremic neuropathy may be susceptible to succinylcholine-induced hyperkalemia, although evidence supporting this view is scarce.[107][112]

Severe hyperkalemia may follow the administration of succinylcholine to patients with severe metabolic acidosis and hypovolemia.[113] In rabbits, the combination of metabolic acidosis and hypovolemia results in a high resting potassium level and an exaggerated hyperkalemic response to succinylcholine.[114] In this situation, the potassium originates from the gastrointestinal tract and not from muscle, as in the classic hyperkalemic response.[115] In patients with metabolic acidosis and hypovolemia, correction of the acidosis by hyperventilation and sodium bicarbonate administration should be attempted before administration of succinylcholine. Should severe hyperkalemia occur, it can be treated with immediate hyperventilation, 1.0 to 2.0 mg calcium chloride intravenously, 1 mEq/kg sodium bicarbonate, and 10 U regular insulin in 50 mL 50% glucose for adults or, for children, 0.15 U/kg regular insulin in 1.0 mL/kg 50% glucose.

Kohlschütter and colleagues[116] found that four of nine patients with severe abdominal infections had an increase in serum potassium concentrations of as much as 3.1 mEq/L above baseline values after succinylcholine administration. These investigators found that in the case of intra-abdominal infections that persist for longer than 1 week, the possibility of a hyperkalemic response to succinylcholine should be considered.

Stevenson and Birch[117] described a single, well-documented case of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis.

In studying soldiers who had undergone trauma during the Vietnam War, Birch and associates[118] found that a significant increase in serum potassium did not occur in 59 patients until about 1 week after the injury, at which time a progressive increase in serum potassium occurred after the infusion of succinylcholine. Three weeks after injury, three of these patients with especially severe injuries showed marked hyperkalemia with an increase

in serum potassium of greater than 3.6 mEq/L, sufficient to cause cardiac arrest. Birch and coworkers[118] found that prior administration of 6 mg dTc prevented the hyperkalemic response to succinylcholine. In the absence of infection or persistent degeneration of tissue, a patient is susceptible to the hyperkalemic response probably for at least 60 days after massive trauma or until adequate healing of damaged muscle has occurred.

In addition, patients with any number of conditions that have resulted in the proliferation of extrajunctional acetylcholine receptors, such as those with neuromuscular disease, are likely to have an exaggerated hyperkalemic response after the administration of succinylcholine. The response of these patients to neuromuscular blocking agents is reviewed in detail later in this chapter. Some of these disease states include cerebrovascular accident with resultant hemiplegia or paraplegia, muscular dystrophies, and Guillain-Barré syndrome. The hyperkalemia after administration of succinylcholine may be to such an extent that cardiac arrest ensues. For an in-depth discussion of the clinical and pathophysiologic aspects of succinylcholine-induced hyperkalemia, the reader is referred to a review by Gronert and Theye.[119]

Increased Intraocular Pressure (also see Chapter 65)

Succinylcholine usually causes an increase in intraocular pressure (IOP). The increased IOP is manifested within 1 minute after injection, peaks at 2 to 4 minutes, and subsides by 6 minutes.[120] The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils or transient dilatation of choroidal blood vessels, or both. Sublingual administration of nifedipine has been reported to attenuate the increase in IOP from succinylcholine, thus suggesting a circulatory mechanism.[121] Despite this increase in IOP, the use of succinylcholine for ophthalmic procedures is not contraindicated unless the anterior chamber is open. Although Meyers and coworkers[122] were unable to confirm the efficacy of precurarization in attenuating increases in IOP after succinylcholine, numerous other investigators have found that previous administration of a small dose of nondepolarizing neuromuscular blocker (such as 3 mg dTc or 1 mg pancuronium) will prevent a succinylcholine-induced increase in IOP.[123] Furthermore, Libonati and coauthors[124] described the anesthetic management of 73 patients with penetrating eye injuries who received succinylcholine with no loss of global contents. Thus, despite the potential concerns of Meyers and coworkers,[122] Libonati and colleagues[124] found that the use of succinylcholine, after pretreatment with a nondepolarizing neuromuscular blocker, in patients with penetrating eye injuries with a carefully controlled rapidsequence induction of anesthesia is an acceptable technique. Succinylcholine is only one of many factors, such as endotracheal intubation and "bucking" on the endotracheal tube, that may increase IOP.[122] Of prime importance is ensuring that the patient is well anesthetized and is not straining or coughing. Because nondepolarizing neuromuscular blockers with shorter times to onset of effect are now available, providing an anesthetic that allows for the trachea to be intubated rapidly without administering succinylcholine is now an option. Finally, should a patient's anesthesia become too light over the course of intraocular surgery, succinylcholine should not be given to immobilize the patient. Rather, the surgeon should be asked to pause while anesthesia is deepened. If necessary, the depth of neuromuscular blockade can also be increased with nondepolarizing relaxants.[125] In fact, coughing or "bucking" during a vitrectomy may cause serious

postoperative eye damage with marked damage to vision.[126] Adequate anesthesia, with or without paralysis, is essential during eye surgery (also see Chapter 65 and Chapter 82).

Increased Intragastric Pressure

Unlike the rather consistent increase in IOP, the increase in intragastric pressure (IGP) caused by succinylcholine is quite variable. The increase in IGP from succinylcholine is presumed to be due to fasciculations of abdominal skeletal muscle, which is not surprising because more coordinated abdominal skeletal muscle activity (e.g., straight leg raising) may increase IGP to values as high as 120 cm H_2O. In addition to skeletal muscle fasciculations, the acetylcholine-like effect of succinylcholine may be partly responsible for the observed increases in IGP. Greenan[127] noted consistent increases in IGP of 4 to 7 cm H_2O with direct vagal stimulation.

Miller and Way[128] found that 11 of 30 patients essentially had no increase in IGP after succinylcholine. Nonetheless, 5 of 30 patients had an increase in IGP greater than 30 cm H_2O. The increase in IGP from succinylcholine appeared to be related to the intensity of fasciculations of the abdominal skeletal muscles. Accordingly, when fasciculations were prevented by previous administration of a nondepolarizing neuromuscular blocker, no increase in IGP was observed.

Are the increases in IGP after succinylcholine administration enough to cause incompetence of the gastroesophageal junction? Generally, IGP greater than 28 cm H_2O is required to overcome the competence of the gastroesophageal junction. However, when the normal oblique angle of entry of the esophagus into the stomach is altered, as may occur with pregnancy, an abdomen distended by ascites, bowel obstruction, or a hiatal hernia, the IGP required to cause incompetence of the gastroesophageal junction is frequently less than 15 cm H_2O.[128] In these circumstances, regurgitation of stomach contents after succinylcholine is a distinct possibility, and precautionary measures should be taken to prevent fasciculation. Endotracheal intubation may be facilitated by the administration of a nondepolarizing neuromuscular blocker, or a defasciculating dose of a nondepolarizing relaxant may be administered before succinylcholine.

Apparently, succinylcholine does not increase IGP appreciably in infants and children, possibly because of the minimal or absent fasciculations after administration of succinylcholine in these age groups.[129]

Increased Intracranial Pressure

Succinylcholine has the potential to increase intracranial pressure.[130] The mechanisms and clinical significance of this transient increase are unknown, but the rise in intracranial pressure does not occur after pretreatment with nondepolarizing neuromuscular blockers.[131]

Myalgia

The incidence of muscle pain after administration of succinylcholine varies from 0.2% to 89%.[132] It occurs more frequently after minor surgery, especially in women and

ambulatory rather than bedridden patients.[133] Waters and Mapleson[133] postulated that the pain is secondary to damage produced in muscle by the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis. That damage to muscle may occur has been substantiated by finding myoglobinemia and increases in serum creatine kinase after succinylcholine administration.[134][135][136] Previous administration of a small dose of a nondepolarizing neuromuscular blocker clearly prevents fasciculations from succinylcholine.[134] However, the efficacy of this approach in preventing muscle pain is questionable. Although some investigators claim that pretreatment with a defasciculating dose of a nondepolarizing neuromuscular blocker has no effect,[132] many believe that the pain from succinylcholine is at least attenuated.[135][136][137] Pretreatment with a prostaglandin inhibitor (lysine acetylsalicylate) has been shown to be effective in decreasing the incidence of muscle pain after succinylcholine.[138] This finding suggests a possible role for prostaglandins and cyclooxygenases in succinylcholine-induced myalgias. Other investigators have found that myalgias after outpatient surgery occur even in the absence of succinylcholine.[139][140]

Masseter Spasm (also see Chapter 29 and Chapter 60)

An increase in tone of the masseter muscle is a frequent response to succinylcholine in adults,[141] as well as children.[142][143][144] Meakin and associates[142] suggested that the frequent occurrence of spasm in children may be due to an inadequate dose of succinylcholine. In all likelihood, this increase in tone is an exaggerated contractile response at the neuromuscular junction and cannot be used to establish a diagnosis of malignant hyperthermia. Although an increase in tone of the masseter muscle may be an early indicator of malignant hyperthermia,[145] it is not consistently associated with malignant hyperthermia.[146] Currently, there is no indication to change to a "nontriggering" anesthetic in instances of isolated masseter spasm.[143]

Clinical Uses

In spite of its many adverse effects, succinylcholine is still commonly used. Its popularity is probably due to its rapid onset of effect, the profound depth of neuromuscular blockade that it produces, and its short duration of action. Although it may be less commonly used than in the past for routine endotracheal intubation, it is the neuromuscular blocker of choice for rapid-sequence induction of anesthesia. In a study[147] comparing intubating conditions after 1 mg/kg succinylcholine with those after 0.1 mg/kg vecuronium or 0.1 mg/kg pancuronium at 30 seconds after the administration of a relaxant and at 30-second intervals after that for up to 120 seconds, intubation could be accomplished in all patients receiving succinylcholine at 30 seconds, in contrast to the other neuromuscular blockers studied. Furthermore, at all time points studied, up to 90 seconds, intubating conditions were better after the administration of succinylcholine than after either of the other two neuromuscular blockers. Although 1.0 mg/kg succinylcholine has long been recommended to facilitate endotracheal intubation at 60 seconds, recovery of neuromuscular function may not occur quickly enough to prevent hemoglobin desaturation in an apneic patient.[148][149] Recent studies have indicated that 0.5 to 0.6 mg/kg succinylcholine should allow for adequate intubating conditions 60 seconds after administration for nonrapid sequence intubation.[150][151]

A small dose of nondepolarizing neuromuscular blocker is commonly given 2 minutes before administering the intubating dose of succinylcholine. This defasciculating dose of nondepolarizing neuromuscular blocker will attenuate increases in intragastric and intracranial pressure, as well as minimize the incidence of fasciculations in response to succinylcholine. The previous administration of a nondepolarizing agent will render the muscle relatively resistant to succinylcholine, and the succinylcholine dose should therefore be increased by 50%.[152] The use of a defasciculating dose of a nondepolarizing neuromuscular blocker may also slow the onset of succinylcholine and produce less favorable conditions for tracheal intubation.[136][137]

Typically after administering succinylcholine for intubation, a nondepolarizing neuromuscular blocker is given to maintain neuromuscular blockade. Succinylcholine given first may enhance the depth of block induced by a subsequent dose of nondepolarizing neuromuscular blocker.[153][154][155] However, the effect on duration of action is variable. Succinylcholine has no effect on pancuronium, pipecuronium, or mivacurium,[155][156] but it increases the duration of atracurium and rocuronium.[153][154] The reasons for these differences are not clear.

The changing characteristics of succinylcholine neuromuscular blockade over the course of prolonged administration have been reviewed by Lee and Katz[157] and are summarized in Table 13-3. TOF stimulation is a very safe and useful guide in detecting the transition from a phase 1 to a phase 2 block. A phase 1 block has all the characteristics of a depolarizing block as described previously in the section on monitoring. A phase 2 block has the characteristics of a nondepolarizing block. With the administration of large doses of succinylcholine, the nature of the block, as determined by a neuromuscular blockade monitor, changes from that of a depolarizing agent to that of a nondepolarizing agent. Clearly, both the dose and the duration of administration of succinylcholine are important variables, although the relative contribution of each has not been established. Practically, if administration of the drug is terminated shortly after TOF fade is clearly evident, rapid return of normal neuromuscular function should ensue. In addition, the decision of whether to attempt antagonism of a phase 2 block has always been controversial. However, if the TOF ratio is less than 0.4, administration of edrophonium or neostigmine should result in prompt antagonism. Ramsey and colleagues[158] recommended that antagonism of a succinylcholine-induced phase 2 block with edrophonium or neostigmine be attempted after spontaneous recovery of the twitch response has been observed for 20 to 30 minutes and has reached a plateau phase with further recovery proceeding slowly. These researchers state that in this situation, edrophonium and neostigmine invariably produce "dramatic" acceleration of the return of the TOF ratio toward normal. Monitoring neuromuscular function with TOF stimuli will help avoid succinylcholine overdose, detect the development of a phase 2 block, observe the rate of recovery of neuromuscular function and assess the effect of edrophonium or neostigmine on recovery.

Table 13-3 -- Clinical characteristics of phase 1 and phase 2 neuromuscular blockade during succinylcholine infusion

Characteristic	Phase 1	Transition	Phase 2

Characteristic	Phase 1	Transition	Phase 2
Tetanic stimulation	No fade	Slight fade	Fade
Post-tetanic facilitation	None	Slight	Yes
Train-of-four	No	Moderate fade	Marked fade
Train-of-four ratio	>0.7	0.4–0.7	<0.4
Edrophonium	Augments	Little effect	Antagonizes
Recovery	Rapid	Rapid to slow	Increasingly prolonged
Dose requirements (mg/kg)*	2–3	4–5	>6
Tachyphylaxis	No	Yes	Yes

* Cumulative dosage of succinylcholine by infusion under nitrous oxide anesthesia supplemented with intravenous agents. The dosage requirement to cause a phase 2 block is less in the presence of potent volatile anesthetics (e.g., isoflurane). Adapted from Lee C, Katz RL: Neuromuscular pharmacology. A clinical update and commentary. Br J Anaesth 52:173–188, 1980.

Interactions with Anticholinesterases

Another interaction with succinylcholine involves neostigmine or pyridostigmine. For example, after dTc has been used for intra-abdominal surgery of long duration and the neuromuscular blockade has been reversed by neostigmine, the surgeon announces that another 15 minutes is needed to retrieve a missing sponge. Succinylcholine should not be administered to reestablish neuromuscular blockade because it produces relaxation that will last up to 60 minutes when given soon after the administration of neostigmine (5 mg). Sunew and Hicks[77] found that the effect of succinylcholine (1 mg/kg) was prolonged from 11 to 35 minutes when it was given 5 minutes after the administration of neostigmine (5 mg). Such prolongation can partly be explained by inhibition of butyrylcholinesterase by neostigmine. Ninety minutes after neostigmine administration, butyrylcholinesterase activity returned to less than 50% of its baseline value.

NONDEPOLARIZING NEUROMUSCULAR BLOCKERS

The use of neuromuscular blocking drugs in anesthesia has its origin in the South American Indians' arrow poisons or curares. Several nondepolarizing neuromuscular blockers are still purified from naturally occurring sources. For example, although dTc can be synthesized, it is still less expensive to isolate it from the Amazonian vine *Chondodendron tomentosum*. Similarly, the intermediates for the production of metocurine and alcuronium, which are semisynthetic, are obtained from *Chondodendron* and *Strychnos toxifera*. Malouetine, the first steroidal neuromuscular blocking drug, was originally isolated from *Malouetia bequaertiana,* which grows in the jungles of Zaire in central Africa. Pancuronium, vecuronium, pipecuronium, rocuronium, rapacuronium, atracurium, doxacurium, mivacurium, cisatracurium, and gallamine are entirely synthetic.

The available nondepolarizing neuromuscular blockers can be classified according to chemical class (steroidal, benzylisoquinolinium, or other compounds) or according to onset

or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses (Table 13-4).

Table 13-4 -- Classification of nondepolarizing neuromuscular blockers according to duration of action (time to T1 = 25% of control) after2 × ED_{95} dose

	Clinical Duration			
	Long Acting (>50 min)	***Intermediate Acting (20–50 min)***	***Short Acting (10–20 min)***	***Ultrashort Acting (<10 min)***
Steroidal compounds	Pancuronium	Vecuronium	Rapacuronium	
	Pipecuronium	Rocuronium		
Benzylisoquinolinium compounds	*d*-Tubocurarine	Atracurium	Mivacurium	
	Metocurine	Cisatracurium		
	Doxacurium			
Others				
Asymmetric mixed-onium chlorofumarates				430A
Bisquaternary tropinyl diester				TAAC3
Phenolic ether	Gallamine			
Diallyl derivative of toxiferine	Alcuronium			
Most nondepolarizing neuromuscular blockers are bisquaternary ammonium compounds. *d*-Tubocurarine, vecuronium, rocuronium, and rapacuronium are monoquaternary compounds, and gallamine is a trisquaternary ammonium compound.				

Structure-Activity Relationships

Nondepolarizing neuromuscular blocking drugs were originally classified by Bovet[61] as pachycurares, or bulky molecules having the amine functions incorporated into rigid ring structures. Two extensively studied chemical series of synthetic nondepolarizing neuromuscular blockers are (1) the aminosteroids (steroidal), in which the distance is maintained by an androstane skeleton, and (2) the benzylisoquinolinium series, in which the distance is maintained by linear diester-containing chains or, in the case of curare, by benzyl ethers. For a detailed account of structure-activity relationships, see Lee.[159]

dTc is a neuromuscular blocker in which the amines are present in the form of two benzyl-substituted tetrahydroisoquinoline structures (Fig. 13-7). The quaternary/tertiary nature of the two amines was initially questioned; however, in nuclear magnetic resonance spectroscopy and methylation/demethylation studies, Everett and colleagues[160] demonstrated that dTc contains only three *N*-methyl groups. One amine is quaternary (permanently charged with four nitrogen substituents) and the other tertiary (pH-dependent charge with three nitrogen substituents). At physiologic pH, the tertiary nitrogen is protonated to render it positively charged. The structure-activity relationships of bis-benzylisoquinolines (Fig. 13-7) have been described by Waser[161] and by Hill and associates[162] as follows:

1. The nitrogen atoms are incorporated into isoquinoline ring systems. This bulky molecule favors nondepolarizing rather than depolarizing activity.
2. The interonium distance (distance between charged amines) is approximately 1.4 nm.
3. Both the ganglion-blocking and the histamine-releasing properties of dTc are probably due to the presence of the tertiary amine function.
4. When dTc is methylated at the tertiary amine and at the hydroxyl groups, the result is metocurine, a compound with greater potency (by a factor of 2 in humans) but much weaker ganglion-blocking and histamine-releasing properties than dTc has (see Fig. 13-7). Metocurine contains three additional methyl groups, one of which quaternizes the tertiary nitrogen of dTc; the other two form methyl ethers at the phenolic hydroxyl groups.
5. Bisquaternary compounds are more potent than their monoquaternary analogs.[163] The bisquaternary derivative of dTc (chondocurine) has more than double the potency of dTc (see Fig. 13-7).
6. Substitution of the methyl groups on the quaternary nitrogen with bulkier groups causes a reduction in both potency and duration of action.

Figure 13-7 Chemical structure of *d*-tubocurarine, metocurine, and chondocurine.

Atracurium is a bis-benzyltetrahydroisoquinolinium with isoquinolinium nitrogens connected by a diester-containing hydrocarbon chain (Fig. 13-8). The presence (in duplicate) of two-carbon separations between quaternary nitrogen and ester carbonyl provides the substrate for a Hofmann degradation reaction.[9][164] In a Hofmann elimination reaction, a quaternary ammonium group is converted into a tertiary amine by cleavage of a carbon-nitrogen bond. This reaction is pH and temperature dependent, with higher pH and temperature favoring elimination. The actual structure of the quaternary centers is the

laudanosinium moiety as in metocurine. Atracurium has four chiral centers at each of the adjacent chiral carbons of the two amines. The marketed product has 10 isomers.[164][165] These isomers have been separated into three geometric isomer groups that are designated *cis-cis, cis-trans,* and *trans-trans* based on their configuration about the tetrahydroisoquinoline ring system.[164][165] The ratio of the *cis-cis, cis-trans,* and *trans-trans* isomers is approximately 10:6:1, which corresponds to about 50% to 55% *cis-cis,* 35% to 38% *cis-trans,* and 6% to 7% *trans-trans* isomers.[166]

Figure 13-8 Chemical structure of atracurium, cisatracurium, mivacurium, and doxacurium. *Chiral centers *arrows* showing the cleavage sites for Hofmann elimination.

Cisatracurium is the 1R *cis*-1'R *cis* isomer of atracurium and represents about 15% of the marketed atracurium mixture by weight, but more than 50% in terms of potency or neuromuscular blocking activity (see Fig. 13-8). R designates the absolute stereochemistry of benzyltetrahydroisoquinoline rings, and *cis* represents the relative geometry of the bulky dimethoxy and 2-alkyester groups at C(1) and N(1), respectively.[167][168] Cisatracurium is metabolized by Hofmann elimination. It is approximately four times as potent as atracurium, and unlike atracurium, it does not cause histamine release in the clinical dose range.[167][169] This observation indicates that the phenomenon of histamine release may be stereospecific.[167][170] Cisatracurium is the second benzylisoquinolinium (after doxacurium) to be largely free of this side effect.

Mivacurium differs from atracurium by the presence of an additional methylated phenolic group (see Fig. 13-8). When compared with other isoquinolinium neuromuscular blockers, the interonium chain of mivacurium is longer (16 atoms).[162] Mivacurium consists of a mixture of three stereoisomers.[171] The two most active are the *trans-trans* and *cis-trans* isomers (57% and 37% weight per weight [w/w], respectively), which are equipotent; the *cis-cis* isomer (6% w/w) has only a tenth the activity of the others in cats and monkeys.[171] Mivacurium is metabolized by butyrylcholinesterase at about 70% to 88% the rate of succinylcholine to a monoester, a dicarboxylic acid.[10][172]

Doxacurium is a bisquaternary benzylisoquinolinium diester of succinic acid (see Fig. 13-8). The interonium chain is shorter than that in either atracurium or mivacurium. Lee[159] pointed out that the number of methoxy groups on benzylisoquinolinium heads is increased from four (atracurium) and five (mivacurium) to six (doxacurium).[162] This increase was associated with both an increase in potency and a reduction in the propensity to release histamine.[159][162]

Steroidal Neuromuscular Blockers

In the steroidal compounds, it is probably essential that one of two nitrogen atoms in the molecule be quaternized.[173] The presence of acetyl ester (acetylcholine-like moiety) is thought to facilitate its interaction with nAChRs at the postsynaptic muscle membrane.[27][174]

Pancuronium is characterized by the presence of two acetyl ester groups on the A and D rings of the steroidal molecule. Pancuronium is a potent neuromuscular blocking drug with both vagolytic and butyrylcholinesterase-inhibiting properties (Fig. 13-9).[175] Deacetylation of the 3-OH or 17-OH groups decreases its potency.[176]

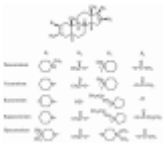

Figure 13-9 Chemical structure of different steroidal neuromuscular blockers.

Vecuronium is an *N*-demethylated derivative of pancuronium in which the 2-piperidine substituent is not methylated (vecuronium lacks the *N*-methyl group at position 2) (see Fig. 13-9).[7][27] At physiologic pH, the tertiary amine is largely protonated similar to dTc. The minor molecular modification in comparison to pancuronium resulted in (1) a slight change in the potency; (2) a marked reduction in vagolytic properties; (3) molecular instability in solution, which explains in part the shorter duration of action of vecuronium than pancuronium; and (4) increased lipid solubility, which results in greater biliary elimination of vecuronium than pancuronium.[27][162]

Pancuronium and vecuronium are very similar in structure, yet vecuronium is prepared as a lyophilized powder. Vecuronium is degraded by the hydrolysis of either (or both) acetyl esters at the C3- and C17-positions. Hydrolysis at the C3-position is the primary degradation product. The acetate at the 3-position is more susceptible to hydrolysis in aqueous solutions. Vecuronium is less stable in solution because the group effect of the adjacent basic piperidine at the 2-position facilitates hydrolysis of the 3-acetate. Therefore, vecuronium cannot be prepared as a ready-to-use solution with a sufficient shelf life, even as a buffered solution.[177] In pancuronium, the 2-piperidine is quaternized and no longer basic. Thus, it does not participate in catalysis of the 3-acetate hydrolysis.[177]

Pipecuronium, like pancuronium, is a bisquaternary compound. Pipecuronium has piperazine rings attached to the A and D rings of the steroid nucleus, whereas pancuronium has piperidine rings (see Fig. 13-9).[162] Pipecuronium is a nonvagolytic substitute for pancuronium. Changes in the quaternary groups, in which the quaternary nitrogen atoms were placed at the distal (4-position) aspect of the 2,16-β substitutions, lessen the vagolytic effects.[162] As a result, pipecuronium is about 10 times less vagolytic than pancuronium.

Rocuronium lacks the acetyl ester that is found in the steroid nucleus of pancuronium and vecuronium in the A ring (see Fig. 13-9). The introduction of cyclic substituents other than piperidine at the 2- and 16-positions resulted in a fast-onset compound.[178] The methyl group attached to the quaternary nitrogen of vecuronium and pancuronium is replaced by an allyl group in rocuronium and rapacuronium. As a result, rocuronium and rapacuronium are about 6 and 10 times less potent than vecuronium, respectively.[178][179][180] Replacement of the acetyl ester attached to the A ring by a hydroxy group has made it possible to present rocuronium as a stable solution. At room temperature, rocuronium is stable for 60 days, whereas pancuronium is stable for 6 months. The reason for this difference in shelf life is

related to the fact that rocuronium is terminally sterilized in manufacturing and pancuronium is not. Terminal sterilization causes some degree of degradation.[177]

Rapacuronium became available in the United States in 1999 but was withdrawn from the market by the manufacturer in spring 2001 because of a high incidence of respiratory complications.[181][182][183][184] Rapacuronium is a monoquaternary compound that has the same basic steroid backbone as the rest of the steroidal neuromuscular blockers (see Fig. 13-9).

Asymmetric Mixed-Onium Chlorofumarates (430A)

The agent 430A (Fig. 13-10) represents a new class of non-depolarizing neuromuscular blockers called asymmetric mixed-onium chlorofumarates. The presence of three methyl groups between the quaternary nitrogen and oxygen atom at each end of the carbon chain suggests that similar to mivacurium, this compound will not undergo Hofmann degradation.[13][185][186][187] The compound has an ultrashort duration of action in human volunteers and different animal species. A study in anesthetized human volunteers evaluated the onset and recovery profiles of 430A in the thumb and larynx. The pattern of blockade resembles that of succinylcholine, with fully paralyzing doses (2 to 3 × ED_{95} or 0.38 to 0.54 mg/kg) producing 100% block of TOF stimulation within 50 to 60 seconds in the larynx. Spontaneous recovery to a TOF of 0.9 develops in the thumb within about 12 to 15 minutes after the administration of doses as large as 0.54 mg/kg (or3 × ED_{95}). Recovery is accelerated by edrophonium. The cardiovascular changes after rapid (5 second) bolus doses in these volunteers have averaged less than 10% from baseline.[188]

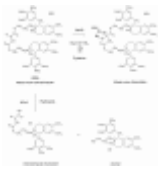

Figure 13-10 Chemical structure of 430A (a mixed-onium chlorofumarate). In whole human blood, two pathways of deactivation occur, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product with cysteine replacing chlorine and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution to chlorofumarate monoester and alcohol.[187]

Bisquaternary Tropinyl Diester Derivatives

TAAC3 is a bis[*N*-(3,4-diacetoxybenzyl)tropanium-3α-yl] glutarate dibromide (Fig. 13-11).[12] No data on this compound in humans have been published. In animals, TAAC3 has a slower onset and shorter duration than succinylcholine has.[189] The short duration of action of TAAC3 is attributed to enzymatic hydrolysis of the acetoxy groups on the quaternary benzyl groups by nonspecific carboxyesterases.[189] At ED_{90} doses, TAAC3 exhibits a moderate degree of cardiac vagal block, and in large doses of5 to 10 × ED_{90}, it produces significant hypotension in the dog that is not related to histamine release.[189] The cardiac vagal blocking effect of TAAC3 in equipotent doses is similar to that of rocuronium.[189]

Figure 13-11 Chemical structure of TAAC3.

Phenolic Ether Derivative

Gallamine is a trisquaternary substance (Fig. 13-12). Its potent vagolytic activity is due to the presence of three positively charged nitrogen atoms. Gallamine was synthesized originally by Bovet[61] as part of an extensive structure-activity study that helped evolve the concepts of "pachycurares" and "leptocurares." Succinylcholine also evolved from this work, for which Bovet received the Nobel Prize.

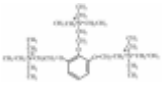

Figure 13-12 Chemical structure of gallamine, a trisquaternary ether of gallic acid. Gallamine is the only trisquaternary compound available. Its strong vagolytic property is probably due to the trisquaternary structure.

Diallyl Derivative of Toxiferine

Introduced in 1964, alcuronium is a long-acting drug that is the semisynthetic diallyl derivative of toxiferine (Fig. 13-13). The latter is purified from *Strychnos toxifera*. Its advantage at the time of its introduction was a relative lack of side effects. It is midly vagolytic and is excreted unchanged by the kidney with a minor secondary biliary pathway. Alcuronium is moderately popular in Europe, the Far East, and Australia, but it is not available in the United States.

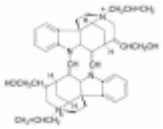

Figure 13-13 Chemical structure of alcuronium, the semisynthetic diallyl derivative of toxiferine. The quaternizing allyl groups actually reduce the potency by a factor of 3 to 5.

Potency of Nondepolarizing Neuromuscular Blockers

Drug potency is commonly expressed by the dose-response relationship. The dose of a neuromuscular blocking drug required to produce an effect (e.g., 50%, 90%, or 95% depression of twitch height; commonly expressed as ED_{50}, ED_{90}, and ED_{95}, respectively) is taken as a measure of the potency of neuromuscular blockers.[10][179][188][190][191][192][193][194][195][196][197][198][199][200][201][202][203][204][205][206][207][208][209][210][211][212][213][214][215][216][217][218][219][220] The drugs have different potencies as illustrated in Table 13-5 and Figure 13-14. For factors affecting the potency of neuromuscular blockers, see the section "Drug Interactions." The dose-response relationship for nondepolarizing neuromuscular blockers is sigmoidal in shape (see Fig. 13-14) and has been derived in a variety of ways. The simplest method is to perform linear regression over the approximately linear portion of a semilogarithmic plot between 25% and 75% neuromuscular block. Alternatively, the curve can be subjected to probit or logit transform to linearize it over its whole length or be subjected to nonlinear regression with the sigmoid Emax model of the form:Effect(e) = .\F($dose_e^{\gamma}$, $dose_e^{\gamma}$ + $dose_{e50}^{\gamma}$)

This equation can be applied to the raw data.[221][222][223] More complex models that relate the concentration of neuromuscular blockers at the neuromuscular junction to their pharmacologic effect have been developed, and they will be discussed later.[224][225]

Table 13-5 -- Dose-response relationships of nondepolarizing neuromuscular blocking drugs in human subjects

	ED_{50} (mg/kg)	ED_{90} (mg/kg)	ED_{95} (mg/kg)	References
Long Acting				
Pancuronium	0.036 (0.022–0.042)	0.056 (0.044–0.070)	0.067 (0.059–0.080)	[179][190]
Pipecuronium	0.021 (0.013–0.032)	0.032 (0.022–0.033)	0.042 (0.024–0.059)	[179][191][192][193][194][195][196]
d-Tubocurarine	0.23 (0.16–0.26)	0.41 (0.27–0.45)	0.48 (0.34–0.56)	[190]
Metocurine	0.14 (0.13–0.15)	0.25 (0.24–0.26)	0.30 (0.28–0.32)	[190]
Doxacurium	0.012 (0.006–0.016)	0.022 (0.021–0.024)	0.024 (0.016–0.033)	[197][198][199][200][201]
Gallamine	1.30	2.30	2.82	[190]
Alcuronium	0.11 (0.07–16)	0.18 (0.12–0.25)	0.22 (0.14–0.29)	[190]
Intermediate Acting				
Rocuronium	0.147 (0.069–0.220)	0.268 (0.200–0.419)	0.305 (0.257–0.521)	[179][202][203][204][205][206][207][208]
Vecuronium	0.027 (0.015–0.031)	0.042 (0.023–0.055)	0.043 (0.037–0.059)	[190]
Atracurium	0.12 (0.08–0.15)	0.18 (0.19–0.24)	0.21 (0.13–0.28)	[190]
Cisatracurium	0.026 (0.015–0.031)	—	0.04 (0.032–0.05)	[209][210][211][212][213]
Short Acting				

	ED_{50} (mg/kg)	ED_{90} (mg/kg)	ED_{95} (mg/kg)	References
Mivacurium	0.039 (0.027–0.052)	—	0.067 (0.045–0.081)	[10][214][215][216][217][218]
Rapacuronium	0.39	—	0.75–1.0	[219][220]
Ultrashort Acting				
430A	0.09	—	0.19	[188]
Data are the median and range of reported values.				
ED_{50}, ED_{90}, and ED_{95}, doses of each drug that produce, respectively, a 50%, 90%, and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle after ulnar nerve stimulation.				

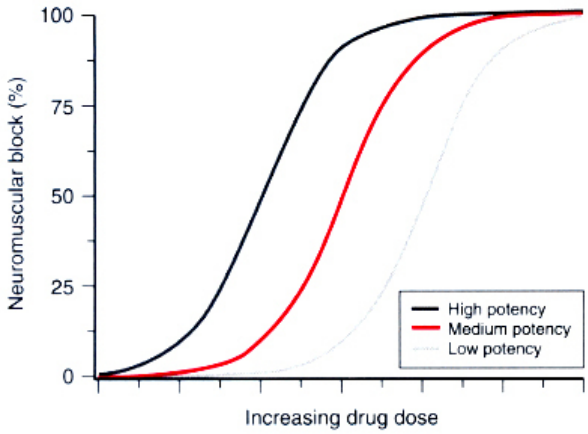

Figure 13-14 Schematic representation of a semilogarithmic plot of muscle relaxant dose versus neuromuscular block. A drug of high potency would be represented by doxacurium, one of medium potency by atracurium, and one of low potency by rocuronium. The graph illustrates that the relative potencies of the muscle relaxants span a range of approximately 2 orders of magnitude.

Pharmacokinetics and Pharmacodynamics

As defined by Wright,[226] pharmacokinetics and pharmacodynamics are "... empirical mathematical model[s] ... that [describe] drug effect time course after administration." In pharmacokinetic modeling, the concept of "compartments" represents different organs/tissues grouped together on the basis of their blood perfusion (high or low). After injection into the circulation, the concentration of a neuromuscular blocker in plasma decreases rapidly at first, then more slowly (Fig. 13-15). The shape of this curve is determined by the processes of distribution and elimination. Classically, this curve is divided into an initial (distribution) phase and a terminal (elimination) phase. This curve can

be represented mathematically by biexponential or triexponential equations[223] in the formConcentration (at time t) = $Ae^{-\alpha t} + Be^{-\beta t}$ (+ $Pe^{-\pi t}$)

These multiexponential equations express the concept of drug being distributed between two or three theoretical compartments.

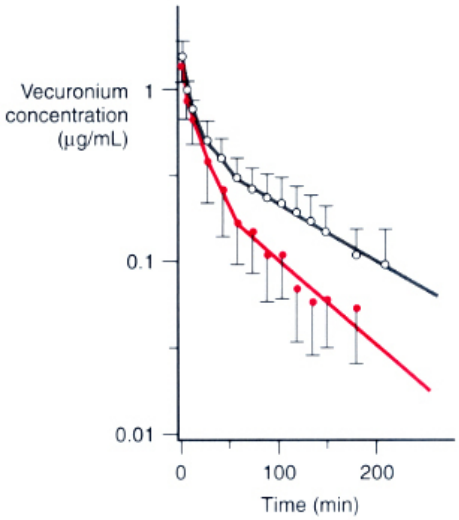

Figure 13-15 Disappearance of vecuronium from plasma after a single bolus dose of 0.2 mg/kg, as illustrated by a semilogarithmic plot of the mean concentration versus time for patients with normal hepatic function *(filled circles)* and cirrhotic patients *(open circles)*. Error bars are the SD for that value.
(Redrawn from Lebrault C, Berger JL, D'Hollander AA, et al: Pharmacokinetics and pharmacodynamics of vecuronium [ORG NC 45] in patients with cirrhosis. Anesthesiology 62:601–605, 1985.)

Figure 13-16 illustrates the classic model whereby drug is administered intravenously into a central compartment with volume V1 and is distributed and eliminated only from this compartment. Drug is distributed very rapidly throughout this central compartment, which includes the plasma volume and the organs of elimination (e.g., in the case of neuromuscular blockers, the kidneys and liver). The "k" terms are the rate constants for drug movement between compartments in the direction of the arrows. The peripheral compartments (usually one or two in number, here represented by V2 and V3) can be thought of as the "tissues." The effect compartment, which will be discussed later, is the neuromuscular junction. For computational purposes, it has infinitesimal volume and therefore does not influence overall drug distribution. Drug administration and elimination are unidirectional; distribution is bidirectional.

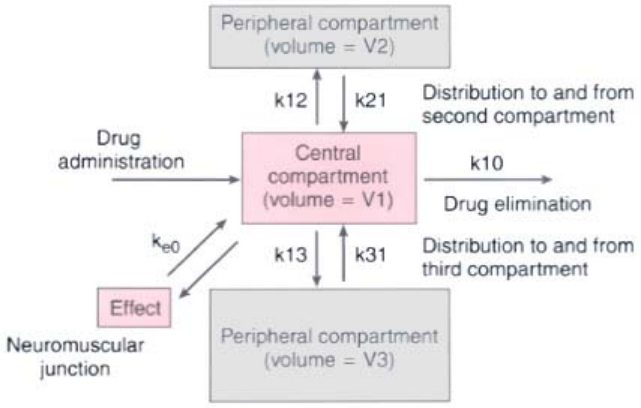

Figure 13-16 Schematic representation of drug disposition into different compartments. These compartments are mathematical concepts only and do not represent real physiologic spaces. The effect compartment in this case would be the neuromuscular junction for computational purposes; it has infinitesimal volume. The terms k_{nm} are the rate constants for drug movement, in the direction of the *arrow*, between these theoretical compartments. See text for further discussion.

Initially, the drug concentration in the central compartment (plasma concentration) will exceed that in the peripheral compartment (tissue concentration), and drug will move from plasma to tissues. Later, as the plasma concentration decreases, it becomes less than the tissue concentration, and the net direction of drug movement is now from tissues to plasma. In general, this conceptual model is appropriate for all the neuromuscular blockers, with the exception of atracurium and cisatracurium, which also undergo elimination (by degradation) from tissues.[227] For simplicity, the following discussion will assume only one peripheral compartment.

Volume of distribution is the volume to which the drug has distributed when the processes of distribution and elimination are in equilibrium. Elimination is represented by the variable plasma clearance, that is, the volume of plasma from which drug is irreversibly and completely eliminated per unit time. For most nondepolarizing neuromuscular blockers, the process of distribution is more rapid than that of elimination, and the initial rapid decline in plasma concentration is due primarily to distribution of the drug to tissues. An exception to this rule is mivacurium, which has such rapid clearance, because of metabolism by butyrylcholinesterase, that elimination is the principal determinant of the initial decline in plasma concentration.[228]

After the initial process of drug distribution to tissues, the plasma concentration falls more slowly (terminal phase). The rate of decrease in plasma concentration during this terminal phase is often expressed in terms of elimination half-life, which equals the natural logarithm of 2 divided by the rate constant of decline (i.e., the slope of the terminal phase). During this terminal phase, the tissue drug concentration exceeds that of plasma, and the rate of decrease in plasma concentration is determined by two factors: the rate at which drug can move from tissues back to plasma and clearance of drug from plasma. In classic theory for

neuromuscular blockers, drug can move rapidly from tissues to plasma, and elimination from plasma (clearance) is the rate-limiting step. For this reason, the terminal portion of the curve is often termed the elimination phase, even though distribution of drug from tissues to plasma is occurring continually throughout. Volume of distribution can also influence the terminal portion of the curve; the greater the volume of distribution, the slower the decline in plasma concentration.

The neuromuscular blockers are polar drugs, and their volume of distribution is classically thought to be limited to a volume roughly equivalent to a portion of the extracellular fluid space, specifically, 150 to 450 mL/kg (see Table 13-14 and Table 13-15).[223] With this model of drug distribution, the potential rate of drug movement from tissues to plasma exceeds the rate of elimination, and plasma clearance is the process that limits the rate of decline in plasma drug concentration. However, some evidence has shown that neuromuscular blockers are distributed more widely, into tissues with low blood flow (e.g., connective tissue),[229] and the true volume of distribution of dTc has been estimated to be as high as 3.4 L/kg and the elimination half-life as long as 40 hours (compare with values in Table 13-14 and Table 13-15).[230] Because the rate of drug movement from such tissues is less than that of plasma clearance, this becomes the rate-limiting step in the rate of decline in plasma drug concentration. This phase only becomes obvious when drug is administered for many days or when sampling is continued for 24 to 96 hours after drug administration. In normal operating room use of neuromuscular blockers, the amount of drug being distributed to this compartment does not affect clinical response to the drug. In conditions in which clearance of the neuromuscular blocker is reduced, such as renal or hepatic disease, it is the terminal portion of the plasma concentration-versus-time curve that is most affected (see Fig. 13-15).[231] The rate of decline in plasma concentration is slowed, and recovery from paralysis is potentially delayed.[231] In conditions associated with an increased distribution volume, such as renal or hepatic disease, early plasma concentrations of drug may be less than those observed when organ function is normal (Fig. 13-17). With a greater volume of distribution, the plasma concentration should be less whereas the total amount of a drug would be greater (see Fig. 13-17). Decreased protein binding of a drug results in a larger distribution volume, but because the degree of protein binding of neuromuscular blockers is low, changes in protein binding will have minimal effect on their distribution.[232]

Table 13-14 -- Pharmacokinetics of neuromuscular blocking drugs in patients with normal renal function or renal failure

	Plasma Clearance (mL/kg/min)		**Volume of Distribution (mL/kg)**		**Elimination Half-Life (min)**		
	Normal Function	***Renal Failure***	***Normal Function***	***Renal Failure***	***Normal Function***	***Renal Failure***	**Reference**
Short-Acting Drugs							
Mivacurium isomers							[314]

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-Life (min)		
	Normal Function	*Renal Failure*	*Normal Function*	*Renal Failure*	*Normal Function*	*Renal Failure*	Reference
Cis-trans	106	80	278	475	2.0	4.3	
Trans-trans	57	48	211	270	2.3	4.3	
Cis-cis	3.8	2.4*	227	244	68	80	
Intermediate-Acting Drugs							
Atracurium	6.1	6.7	182	224	21	24	[348]
	5.5	5.8	153	141	19	20	[349]*†
	10.9	7.8	280	265	17.3	19.7	[705]
Cisatracurium	5.2	—	31	—	—	—	[342]
Vecuronium	3.0	2.5	194	239	78	97	[706]
	3.2	2.6	510	471	117	149	[707]
	3.6	4.5	242	347	51	68	[708]
	5.3	3.1*	199	241	53	83*	[709]
Rocuronium	2.9	2.9	207	264*	71	97*	[352]
Long-Acting Drugs							
d-Tubocurarine	2.4	1.5	250	250	84	132	[224]
Metocurine	1.2	0.4*	472	353	300	684*	[345]
Doxacurium	2.7	1.2*	220	270	99	221*	[346]
Pancuronium	74	20*	148	236*	97	475*	[233]†
	1.7	0.9	261	296*	132	257*	[295]
Pipecuronium	2.4	1.6*	309	442*	137	263*	[298]
Gallamine	1.20	0.24*	240	280	132	750*	[347]

* Significant difference between normal renal function and renal failure.

† Values expressed as milliliters per minute, not weight adjusted.

Table 13-15 -- Pharmacokinetics of neuromuscular blocking drugs in patients with normal liver function or hepatobiliary disease

	Plasma Clearance (mL/kg/min)		Volume of Distribution (mL/kg)		Elimination Half-Life (min)			
	Normal	*Disease*	*Normal*	*Disease*	*Normal*	*Disease*	Hepatic Pathology	Reference
Short-Acting Drugs								
Mivacurium isomers							Cirrhosis	[172]
Cis-trans	95	44*	210	188	1.53	2.48*		
Trans-trans	70	32*	200	199	2.32	11.1*		
Cis-cis	5.2	4.2	266	237	50.3	60.8		
Intermediate-Acting Drugs								
Atracurium	5.3	6.5	159	207*	21	22	Hepatorenal	[712]
	6.6	8.0*	202	282*	21	25	Cirrhosis	[330]
Cisatracurium	5.7	6.6*	161	195*	23.5	24.4	Transplantation	
Vecuronium	4.26	2.73*	246	253	58	84*	Cirrhosis	[231]
	4.30	2.36*	247	206	58	98*	Cholestasis	[731]
	4.5	4.4	180	220	58	51	Cirrhosis	[304]
Rocuronium	2.79	2.41	184	234	87.5	96.0	Cirrhosis	[353]
	217	217	16.4	23.4*	76.4	111.5*	Mixed	[356]†
	296	189	151	264*	56	98*	Cirrhosis	[732]†
	3.70	2.66*	211	248	92	143*	Cirrhosis	[357]
Long-Acting Drugs								
Doxacurium	2.7	2.3	220	290	99	115	Transplantation	[346]
Pancuronium	123	59*	261	307*	133	267*	Cholestasis	[296]†
	1.86	1.45*	279	416*	114	208*	Cirrhosis	[294]
	1.76	1.47	284	425*	141	224*	Cholestasis	[732]
Pipecuronium	3.0	2.6*	350	452	111	143	Cirrhosis	[299]
Gallamine	1.22	0.90	237	259	162	220	Cholestasis	[733]
	1.20	1.21	206	247*	135	160	Cholestasis	[734]

* Significant difference between normal hepatic function and hepatobiliary disease.

† Values expressed as milliliters per minute, or liters, not weight adjusted.

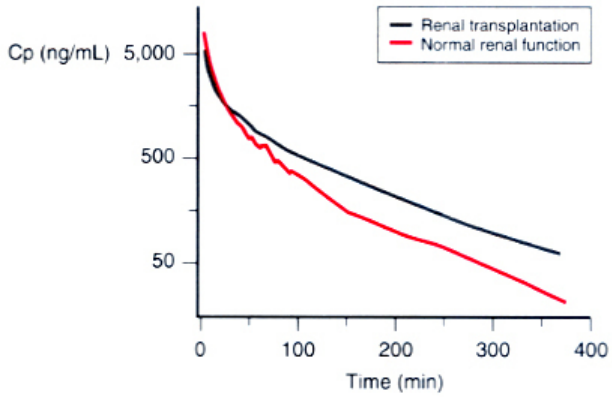

Figure 13-17 "Average" plasma concentration (Cp) versus time after 0.6 mg/kg rocuronium in patients with normal renal function or patients undergoing renal transplantation.
(Redrawn from Szenohradszky J, Fisher DM, Segredo V, et al: Pharmacokinetics of rocuronium bromide [ORG 9426] in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899–904, 1992.)

Recovery of neuromuscular function takes place as plasma concentrations decline. The greater part of this decline occurs primarily because of distribution. Thus, processes that primarily affect elimination of the drug, such as renal failure, may not be associated with a prolonged duration of block.[233][234] However, as recovery comes to rely more on drug elimination than distribution, that is, recovery from 25% to 75% or more or after the administration of larger or repeated doses, the duration of action may be prolonged.[227][235]

After injection of a neuromuscular blocker, the plasma drug concentration immediately starts to decrease. The effect (neuromuscular blockade) takes approximately 1 minute to begin, increases initially, and does not begin to recover for many more minutes despite continually decreasing plasma concentrations of drug. This discrepancy between plasma concentration and drug effect occurs because the action of neuromuscular blockers is not in plasma but at the neuromuscular junction. To produce paralysis, the drug must diffuse from plasma to the neuromuscular junction, and the effect is terminated later by drug diffusion back into plasma (see Fig. 13-16). Thus, concentrations at the neuromuscular junction lag behind those in plasma, and they are less during onset of block and greater during recovery. The plasma concentration-effect relationship exhibits hysteresis; that is, for a given level of block, plasma concentrations are greater during onset than during recovery. For this reason, a concentration-effect relationship cannot be obtained simply by directly relating plasma concentration to the level of neuromuscular blockade.

To overcome this problem, pharmacodynamic models have been developed to incorporate a factor for the delay caused by drug diffusion to and from the neuromuscular junction.[153][224][236][237][238][239][240][241][242][243][244][245][246][247] This factor, k_{e0}, is the rate constant for drug equilibration between plasma and the neuromuscular junction. By

measuring plasma drug concentrations and neuromuscular blockade duringboth the onset and recovery phases and by using the technique of simultaneous pharmacokinetic/pharmacodynamic modeling, it is possible to collapse the hysteresis in the plasma concentration-effect curve, estimate actual neuromuscular junction drug concentrations, and derive true concentration-effect relationships (CE_{50} and k_{e0}) for the neuromuscular blockers (Table 13-6).[224]

Table 13-6 -- Pharmacodynamic parameters derived from simultaneous pharmacokinetic/pharmacodynamic modeling

		Adductor Pollicis		
	Study Group	***CE_{50}* (ng/mL)***	***k_{e0}† (min^{-1})***	**Reference**
Mivacurium				
Central link		57	0.169	[236]
Peripheral link		130	0.101	[236]
Rocuronium	Adult female	684	0.329	[237]
	Propofol-remifentanil anesthesia			
	Standard model			
	Recirculatory model	876	0.129	[237]
	Volunteers	3510	0.405	[238]
	Propofol-fentanyl anesthesia			
	Infants	1190	0.25	[239]
	Children	1650	0.32	[239]
Cisatracurium	Adults	126–158	0.07–0.09	[240]
0.075–3.0 mg/kg	Propofol-fentanyl anesthesia			
Atracurium	Infants	363	0.19	[241]
	Children	444	0.16	[241]
	Young adults	449	0.13	[242]
	Elderly adults	436	0.12	[242]
	Standard model	359	0.12	[243]
	Threshold model	357	0.12	[243]
	Young adults	669‡	0.07	[244]
	Burn patients	2270‡	0.10	[244]
	No succinylcholine	454‡	0.07	[153]
	After succinylcholine	305‡	0.09	[153]

		Adductor Pollicis		
	Study Group	***CE_{50}* (ng/mL)**	***k_{e0}† (min^{-1})***	**Reference**
Vecuronium	Young adults	94	—	[245]
	Young adults	92	0.17	[246]
	Elderly adults	106	0.17	[246]
d-Tubocurarine	Normal renal function	370	0.13	[224]
	Renal failure	380	0.16	[224]
	Halothane 0.5%–0.7%	360‡	0.09‡	[247]§
	Halothane 1.0%–1.2%	220‡	0.12	[247]§
	Narcotic anesthesia	600‡	0.15‡	[247]§
Pancuronium	Young adults	88	—	[245]

* CE_{50} is the neuromuscular junction concentration (biophase) of each drug that produces a 50% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle after ulnar nerve stimulation.

† k_{e0} is the rate constant for equilibration of drug between plasma and the neuromuscular junction.

‡ All groups different from each other.

§ k_{e0} values calculated as $0.693/t_{½}^{ke0}$.

Clinical Management

Neuromuscular blockers are mainly used to facilitate tracheal intubation and provide surgical relaxation. The required intensity of neuromuscular blockade varies with the surgical procedure. In practice, important safety issues with neuromuscular blockers are cardiovascular and respiratory side effects and the adequacy of recovery to normal neuromuscular function.

Several clinical alternatives to neuromuscular blockers are available to provide adequate surgical relaxation. It is important to keep them all in mind to avoid relying only on neuromuscular blockade to achieve a desired degree of relaxation. These options include adjustment of the depth of general anesthesia, regional anesthesia, proper positioning of the patient on the operating table, and proper adjustment of the depth of neuromuscular blockade. The choice of one or several of these options is determined by the estimated remaining duration of surgery, the anesthetic technique, and the surgical maneuver required.

Dosage

General Dosage Guidelines

It is important to select the proper dose of a nondepolarizing neuromuscular blocker to ensure that the desired effect is achieved without excessive overdosage. In addition to a general knowledge of the guidelines, precise practice requires the use of a peripheral nerve stimulator to adjust the relaxant dosage to the individual patient. Overdosage must be avoided for two reasons: (1) to limit the duration of drug effect to match the anticipated length of surgery and (2) to avoid unwanted cardiovascular side effects.

Initial and Maintenance Dosage

The initial dosage is determined by the purpose of administration. Traditionally, doses used to facilitate tracheal intubation are2 × ED_{95} (this dose also approximates to4 × ED_{50}) (Table 13-7). If the trachea has already been intubated without a nondepolarizing blocker or with succinylcholine and the purpose is simply to produce surgical relaxation, a dose slightly less than the ED_{95} (Table 13-8) should be given, with adjustment upward as indicated by responses evoked by peripheral nerve stimulation. Downward adjustment of the initial dose is necessary in the presence of any of the potent inhaled anesthetics (see the section "Drug Interactions").

Table 13-7 -- Guide to nondepolarizing relaxant dosage (mg/kg) under different anesthetic techniques*

				Dosage for Relaxation	
	ED_{95} under N_2O/O_2	**Dose for Intubation**	**Supplemental Dose after Intubation**	***N_2O***	***Volatile Anesthetic†***
Long Acting					
Pancuronium	0.07	0.08–0.12	0.02	0.05	0.03
Metocurine	0.28	0.3–0.4	0.05	0.2	0.1
d-Tubocurarine	0.5	0.5–0.6	0.1	0.3	0.15
Gallamine	3.0	4.0–6.0	0.5	2.0	1.0
Alcuronium	0.25	0.3	0.05	0.2	0.08
Doxacurium	0.025	0.05–0.08	0.005–0.01	0.025	0.02
Pipecuronium	0.05	0.08–0.1	0.01–0.015	0.04	0.03
Intermediate Acting					
Vecuronium	0.05	0.1–0.2	0.02	0.05	0.03
Atracurium	0.23	0.5–0.6	0.1	0.3	0.15
Cisatracurium	0.05	0.15–0.2	0.02	0.05	0.04
Rocuronium	0.3	0.6–1.0	0.1	0.3	0.15
Short Acting					
Mivacurium	0.08	0.2–0.25	0.05	0.1	0.08
Continuous infusions (µg/kg/min) required to maintain 90%–95% twitch inhibition under N_2O/O_2 with intravenous agents					
Mivacurium	3–15				
Atracurium	4–12				

				Dosage for Relaxation	
	ED_{95} under N_2O/O_2	**Dose for Intubation**	**Supplemental Dose after Intubation**	***N_2O***	***Volatile Anesthetic*†**
Cisatracurium	1–2				
Vecuronium	0.8–1				
Rocuronium	9–12				

* Suggested dosages provide good intubating conditions under light anesthesia. Satisfactory abdominal relaxation may be achieved at the dosages listed after intubation without a relaxant or with succinylcholine. This table is intended as a general guide to dosage. Individual relaxant requirements should be confirmed with a peripheral nerve stimulator.

† Potentiation of nondepolarizing relaxants by different volatile anesthetics has been reported to vary 20% to 50%. Recent data suggest, however, that this variation may be much less, particularly in the case of intermediate- and short-acting relaxants. Therefore, for the sake of simplicity, this table assumes a potentiation of 40% in the case of all volatile anesthetics.

Table 13-8 -- Pharmacodynamic effects of succinylcholine and nondepolarizing neuromuscular blockers

	Anesthesia	**Intubating Dose (mg/kg)**	**Approximate ED_{95} Multiples**	**Maximum Block (%)**	**Time to Maximum Block (min)**	**Clinical Duration * (min)**	**Reference**
Succinylcholine	Narcotic or halothane	0.5	1.7	100	—	6.7	[70]
Succinylcholine	Desflurane	0.6	2	100	1.4	7.6	[151]
Succinylcholine	Narcotic or halothane	1.0	3	100	—	11.3	[70]
Succinylcholine	Desflurane	1.0	3	100	1.2	9.3	[151]
Succinylcholine	Narcotic	1.0	3	—	1.1	8	[248]
Succinylcholine	Narcotic	1.0	3	—	1.1	9	[249]
Succinylcholine	Isoflurane	1.0	3	100	0.8	9	[250]
Steroidal Compounds							
Rocuronium	Narcotic	0.6	2	100	1.7	36	[251]
Rocuronium	Isoflurane	0.6	2	100	1.5	37	[250]

	Anesthesia	Intubating Dose (mg/kg)	Approximate ED_{95} Multiples	Maximum Block (%)	Time to Maximum Block (min)	Clinical Duration * (min)	Reference
Rocuronium	Isoflurane	0.9	3	100	1.3	53	[250]
Rocuronium	Isoflurane	1.2	4	100	0.9	73	[250]
Vecuronium	Isoflurane	0.1	2	100	2.4	41	[250]
Vecuronium	Narcotic	0.1	2	100	2.4	44	[252]
Pancuronium	Narcotic	0.08	1.3	100	2.9	86	[253][254]
Pancuronium	Narcotic	0.1	1.7	99	4	100	[255]
Pipecuronium	Narcotic	0.05	1	93	6.3	29	[194]
Pipecuronium	Narcotic	0.06	1.2	96	5.4	45	[256]
Pipecuronium	Narcotic	0.08	1.6	99	3.9	74	[256]
Pipecuronium	Narcotic	0.1	2	100	3.6	94	[256]
Benzylisoquinolinium Compounds							
Mivacurium	Narcotic	0.15	2	100	3.3	16.8	[10]
Mivacurium	Narcotic	0.15	2	100	3	14.5	[251]
Mivacurium	Halothane	0.15	2	100	2.8	18.6	[217]
Mivacurium	Narcotic	0.2	2.6	100	2.5	19.7	[10]
Mivacurium	Narcotic	0.25	3.3	100	2.3	20.3	[10]
Mivacurium	Narcotic	0.25	3.3	—	2.1	21	[249]
Atracurium	Narcotic	0.5	2	100	3.2	46	[209]
Cisatracurium	Narcotic	0.1	2	99	7.7	46	[257]
Cisatracurium	Narcotic	0.1	2	100	5.2	45	[209]
Cisatracurium	Narcotic	0.2	4	100	2.7	68	[209]
Cisatracurium	Narcotic	0.4	8	100	1.9	91	[209]
Doxacurium	Narcotic	0.04	1.6	100	7.6	77.4	[198]
Doxacurium	Narcotic	0.05	2	100	4.5	125	[198]
Doxacurium	Narcotic	0.06	2.4	100	4.4	123	[198]
d-Tubocurarine	Narcotic	0.6	1.2	97	5.7	81	[255]
Metocurine	Narcotic	0.4	1.3	99	4.1	107	[255]
Diallyl Derivative of Toxiferine							

	Anesthesia	Intubating Dose (mg/kg)	Approximate ED_{95} Multiples	Maximum Block (%)	Time to Maximum Block (min)	Clinical Duration * (min)	Reference
Alcuronium	Narcotic	0.25	1.4	100	2.2	54	[258]
For atracurium and mivacurium, slower injection (30 seconds) is recommended to minimize circulatory effects.							

* Time from injection of the intubating dose to recovery of twitch to 25% of control.

To avoid prolonged residual paralysis or inadequate antagonism of residual blockade, or both, the main goal should be to use the lowest possible dose that will provide adequate relaxation for surgery. Management of individual patients should always be guided by monitoring with a peripheral nerve stimulator. In an adequately anesthetized and monitored patient, there is little reason to completely abolish twitch or TOF responses to peripheral nerve stimulation during maintenance of relaxation. Supplemental (maintenance) doses of neuromuscular blockers should be about a fourth (in the case of intermediate- and short-acting neuromuscular blockers) to a tenth (in case of long-acting neuromuscular blockers) the initial dose and should not be given until clear evidence of initiation of recovery from the previous dose is apparent.

Maintenance of relaxation by continuous infusion of intermediate- and short-acting drugs can be performed and is useful to keep relaxation smooth and to rapidly adjust the depth of relaxation to surgical needs. The depth of block in each patient is kept moderate, if possible, to ensure prompt spontaneous recovery or easy reversal at the end of the procedure. Table 13-7 lists approximate dose ranges that are usually required during infusion to maintain 90% to 95% block of the twitch (one twitch visible on TOF stimulation) under nitrous oxide-oxygen anesthesia supplemented with intravenous anesthetics. The infusion dosage is usually decreased by about 30% to 50% in the presence of potent inhaled anesthetics.

Neuromuscular Blockers and Tracheal Intubation

Speed of onset of a neuromuscular block is one of the requirements to rapidly secure the airway, and it is affected by several factors, including the rate of delivery of the drug to the neuromuscular junction, receptor affinity, plasma clearance, and the mechanism of neuromuscular blockade (depolarizing versus nondepolarizing).[176][259][260] The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blockers.[176][259] A high ED_{95} (low potency) is predictive of rapid onset and vice versa (see Table 13-8 and Fig. 13-18). Except for atracurium,[261] molar potency (the ED_{50} or ED_{95} expressed in μM/kg) is highly predictive of a drug's initial rate of onset of effect (at the adductor pollicis).[259] It should be noted that a drug's measured molar potency is the end result of many contributing factors: the drug's intrinsic potency (the CE_{50}, or the biophase concentration resulting in 50% twitch depression), the rate of equilibration between plasma and the biophase (k_{e0}), the initial rate of plasma clearance, and probably other factors as well.[262] Rocuronium has a molar potency ($ED_{95} \approx 0.54$ μM/kg) that is about 13% that of

vecuronium and only 9% that of cisatracurium. Thus, rapid onset of rocuronium (at the adductor pollicis) is not unexpected.

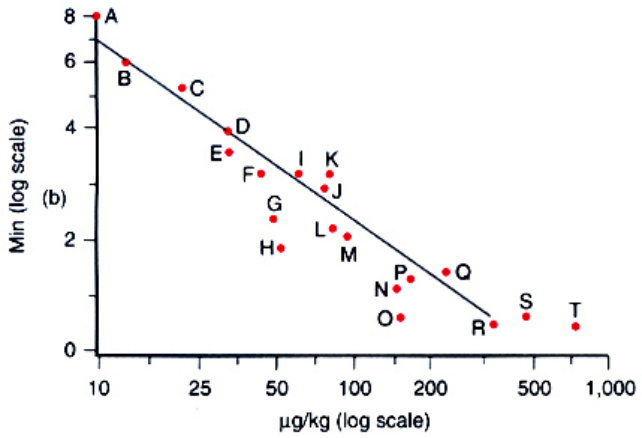

Figure 13-18 Linear regression of the onset of neuromuscular blockade (ordinate) versus potency of a series of steroidal relaxants studied in the cat model by Bowman and colleagues.[176] The data show that onset may be increased in compounds with low potency and encouraged the eventual development of rocuronium and rapacuronium. A, pipecuronium; C, pancuronium; D, vecuronium.

Donati and Meistelman[260] proposed a model to explain the inversed potency-onset relationship. Nondepolarizing neuromuscular blockers of low potency (such as rocuronium and rapacuronium) have more molecules to diffuse from the central compartment into the effect compartment. Once in the effect compartment, all molecules act promptly. Weaker binding of low-potency drugs to receptors prevents buffered diffusion,[260] a process that occurs with potent drug. Buffered diffusion causes repetitive binding and unbinding to receptors, thereby keeping potent drugs in the neighborhood of effector sites and potentially lengthening the duration of effect.

The times to 95% block at the adductor pollicis after a1 × ED_{95} dose of succinylcholine, rocuronium, rapacuronium, vecuronium, atracurium, mivacurium, and cisatracurium are shown in Figure 13-19.[220][259][261] The figure shows that the most potent compound, cisatracurium, has the slowest onset and that the least potent, rocuronium and rapacuronium, are the most rapid (Fig. 13-19).[220][259][261] Bevan[263] also proposed that rapid plasma clearance is associated with a rapid onset of action. The fast onset of succinylcholine is related to its rapid metabolism and plasma clearance.

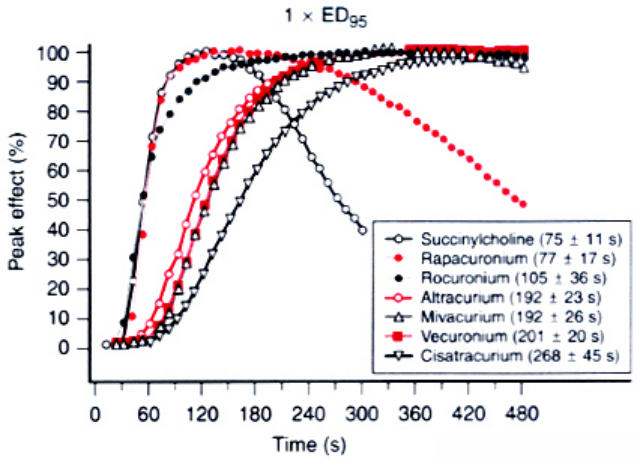

Figure 13-19 Percentage of peak effect after a1 × ED_{95} dose of succinylcholine, rapacuronium, rocuronium, atracurium, mivacurium, vecuronium, and cisatracurium at the adductor pollicis muscle. Times (mean ± SD) in seconds to 95% of peak effect are shown in parentheses.
(Redrawn from Kopman and associates.[220][259][261]*)*

The onset of neuromuscular blockade is much more rapid in the muscles that are relevant to obtaining optimal intubating conditions (laryngeal adductors, diaphragm, and masseter) than in the muscle typically monitored (adductor pollicis) (see Fig. 13-4).[264][265] Neuromuscular blockade develops faster, lasts a shorter time, and recovers more quickly in these muscles (Table 13-9).[46][264][266][267][268] These observations may seem contradictory because there is also convincing evidence that the EC_{50} for almost all drugs studied is between 50% and 100% higher at the diaphragm or larynx than it is at the adductor pollicis. Fisher and coauthors[269] explain this apparent contradiction by postulating more rapid equilibration (shorter $t_{½}k_{e0}$) between plasma and the effect compartment at these central muscles. This accelerated rate of equilibrium probably represents little more than differences in regional blood flow. Muscle blood flow rather than intrinsic potency may be more important in determining the onset and offset time of nondepolarizing neuromuscular blockers.[270] More luxuriant blood flow (greater blood flow per gram of muscle) at the diaphragm or larynx would result in the central muscle receiving a higher peak plasma concentration of drug in the brief period before rapid redistribution is well under way.

Table 13-9 -- Time course of action and peak effect data at the laryngeal adductors and adductor pollicis

		Laryngeal Adductors			Adductor Pollicis			
Dose (mg/kg)	**Anesthesia**	***Onset Time (sec)***	***Maximum Block (% Depression)***	***Clinical Duration * (min)***	***Onset Time (sec)***	***Maximum Block (% Depression)***	***Clinical Duration * (min)***	**Reference**

		Laryngeal Adductors			Adductor Pollicis			
Dose (mg/kg)	**Anesthesia**	***Onset Time (sec)***	***Maximum Block (% Depression)***	***Clinical Duration * (min)***	***Onset Time (sec)***	***Maximum Block (% Depression)***	***Clinical Duration * (min)***	**Reference**
Succinylcholine, 1.0	Propofol-fentanyl	34 ± 12	100 ± 0	4.3 ± 1.6	56 ± 15	100 ± 0	8 ± 2	[266]
Rocuronium, 0.25	Propofol-fentanyl	96 ± 6	37 ± 8	—	180 ± 18	69 ± 8	—	[264]
Rocuronium, 0.4	Propofol-fentanyl	92 ± 29	70 ± 15	—	155 ± 40	99 ± 3	24 ± 7	[266]
Rocuronium, 0.5	Propofol-fentanyl	84 ± 6	77 ± 5	8 ± 3	144 ± 12	98 ± 1	22 ± 3	[264]
Vecuronium, 0.04	Propofol-fentanyl	198 ± 6	55 ± 8	—	342 ± 12	89 ± 3	11 ± 2	[46]
Vecuronium, 0.07	Propofol-fentanyl	198 ± 12	88 ± 4	9 ± 2	342 ± 18	98 ± 1	22 ± 2	[46]
Mivacurium, 0.14	Propofol-alfentanil	137 ± 20	90 ± 7	5.7 ± 2.1	201 ± 59	99 ± 1	16.2 ± 4.6	[267]
Mivacurium, 0.2	Propofol-alfentanil	89 ± 26	99 ± 4	10.4 ± 1.5	202 ± 45	99 ± 2	20.5 ± 3.9	[268]
Values are means and SD[266][267][268] or SEM.[46][264]								

* Clinical duration is the time until T1 recovered to 25% of its control value.

Onset of block in the larynx occurs 1 to 2 minutes earlier than at the adductor pollicis after the administration of nondepolarizing neuromuscular blocking agents. The pattern of blockade (onset, depth, speed of recovery) in the orbicularis oculi is similar to that in the larynx.[271] By monitoring the onset of neuromuscular blockade at the orbicularis oculi, the quality of intubating conditions can be predicted. The onset of maximal block in the larynx also corresponds to the point at which the adductor pollicis is beginning to show palpable evidence of weakening. Furthermore, return of thumb responses to normal suggests that the efferent muscular arc of protective airway reflexes is intact.

Rapid Tracheal Intubation

Succinylcholine remains the drug of choice when rapid tracheal intubation is needed because it consistently provides muscle relaxation within 60 to 90 seconds. When succinylcholine is considered undesirable or contraindicated, the onset of nondepolarizing neuromuscular blocking drugs can be accelerated by preceding the intubating dose with a priming dose of neuromuscular blocker,[272][273][274][275] by the use of high doses of an individual agent,[250][276] or by combinations of neuromuscular blockers.[251][277][278]

Although some combinations of mivacurium and rocuronium can achieve rapid onset without undue prolongation of action and without undesirable effects,[251] combination therapy may not consistently result in rapid onset of effect.[277]

The Priming Technique

Since the introduction of rocuronium, the use of priming has significantly decreased. Several groups of investigators have recommended that a small subparalyzing dose of the nondepolarizer (about 20% of the ED_{95} or about 10% of the intubating dose) be given 2 to 4 minutes before administering a second large dose for tracheal intubation.[272][273][274][275] This procedure, termed *priming,* has been shown to accelerate the onset of block of most nondepolarizing neuromuscular blockers by about 30 to 60 seconds, with the result that intubation can be performed within approximately 90 seconds after the second dose. However, intubating conditions after priming do not match those after succinylcholine.[279] Moreover, priming carries the risk of aspiration and difficulty swallowing, and the visual disturbances associated with subtle degrees of block are uncomfortable for the patient.[280][281]

High-Dose Regimen for Rapid Tracheal Intubation

Larger doses of neuromuscular blockers are usually recommended when intubation must be accomplished in less than 90 seconds. High-dose regimens, however, are associated with considerable prolongation of the duration of action and potentially increased cardiovascular side effects (see Table 13-8).[250][276][282][283] Increasing the dose of rocuronium from0.6 ($2 \times ED_{95}$) to1.2 ($4 \times ED_{95}$) mg/kg shortened the onset time of complete neuromuscular blockade from89 ± 33 seconds (mean ± SD) to55 ± 14 seconds but significantly prolonged the clinical duration (recovery of T1 to 25% of baseline) from37 ± 15 to73 ± 32 minutes, respectively.[250]

Whatever technique of rapid-sequence induction of anesthesia and intubation is elected, the following four principles are important: (1) preoxygenation must be performed, (2) an adequate dosage of intravenous drugs must be administered to ensure that the patient is adequately anesthetized, (3) intubation within 60 to 90 seconds must be considered acceptable, and (4) cricoid pressure should be applied subsequent to injection of the induction agent.

Low-Dose Relaxants for Tracheal Intubation

This low-dose technique is not suitable for rapid-sequence induction. Several studies have demonstrated that low doses of neuromuscular blocking drugs can be used for routine tracheal intubation. A low-dose neuromuscular blocker has several advantages: (1) it shortens the time to recovery from neuromuscular blockade, and (2) it reduces the requirement for anticholinesterase drugs. Rocuronium has the shortest onset time of all the nondepolarizing neuromuscular blocking drugs currently available.[264][266] The maximal effect of either 0.25 or 0.5 mg/kg rocuronium at laryngeal muscles was observed after 1.5 minutes.[264] This interval was shorter than the 3.3 minutes reported after the administration of equipotent doses of vecuronium (0.04 or 0.07 mg/kg)[46] and only slightly more than the 0.9 minute reported after 0.25 or 0.5 mg/kg succinylcholine (see Table 13-9).[284]

With a better understanding of the multiple factors that contribute to satisfactory conditions for intubation, it is now possible to take full advantage of the onset profile for rocuronium. Intubating conditions are related more closely to the degree of neuromuscular blockade of the laryngeal adductor muscles than to the degree of blockade typically monitored at the adductor pollicis. Figure 13-20 demonstrates this principle.[262] Complete block at the larynx or diaphragm, or at both, may not be a prerequisite for satisfactory tracheal intubating conditions.

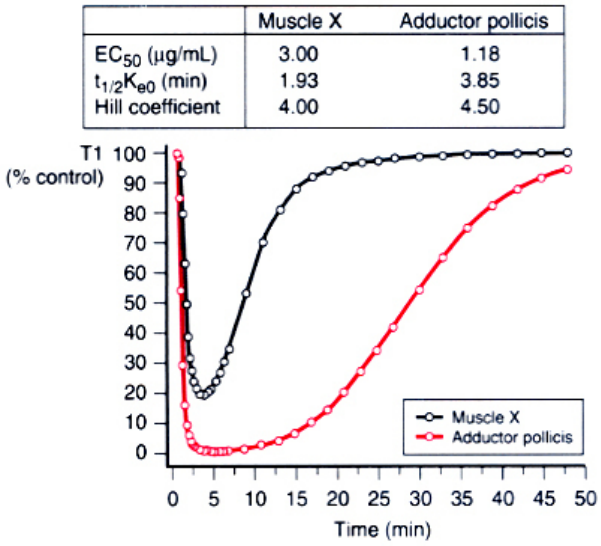

Figure 13-20 A computer simulation based on Sheiner and colleagues' model[224] and data reported by Wierda et al.[285] The ED_{95} of rocuronium at the adductor pollicis from this model is 0.33 mg/kg. Rocuronium, 0.45 mg/kg, is given as a bolus at time zero. Muscle X represents a muscle (such as the diaphragm or the laryngeal adductors) that is less sensitive to the effects of nondepolarizing relaxants than the adductor pollicis is but has greater blood flow. In this example, the concentration of rocuronium producing a 50% block (EC_{50}) of muscle X is 2.5 times that of the adductor pollicis, but the half-life of transport between plasma and the effect compartment ($t_{½}k_{e0}$) of muscle X is only half as long. The rapid equilibration between concentrations of rocuronium in plasma and muscle X results in a more rapid onset of blockade of muscle X than the adductor pollicis. The greater EC_{50} at muscle X explains the faster recovery of this muscle from neuromuscular blockade than the adductor pollicis. Lower blood concentrations of rocuronium must be achieved at the adductor pollicis than at muscle X before recovery begins.
(Redrawn from Naguib M, Kopman AF: Low dose rocuronium for tracheal intubation. Middle East J Anesthesiol 17:193–204, 2003.)

Kopman and colleagues[286] noted that 0.5 mg/kg rocuronium (1.5 × ED_{95}) provided very satisfactory conditions for intubation (25 intubations were rated as excellent and 5 were rated as good) in patients anesthetized with 12.5 µg/kg alfentanil and 2.0 mg/kg propofol if laryngoscopy is delayed for 75 seconds after drug administration. They estimated that a1.5 × ED_{95} dose (0.5 mg/kg) of rocuronium will produce a 95% block or greater in 98% of the population.[286] Others have reported the same observation.[287] It has also been shown that a similar or lower ED_{95} multiple of rocuronium has a more rapid onset and shorter duration than does either atracurium[288] or cisatracurium.[212][289] The onset of cisatracurium is too

slow to provide good conditions for intubation in less than 2 minutes, even after a dose of2 × ED_{95}.[289]

In the vast majority of patients receiving alfentanil, 15 µg/kg, followed by propofol, 2.0 mg/kg, and rocuronium, 0.45 mg/kg, good to excellent conditions for intubation will be present 75 to 90 seconds after the completion of drug administration.[286]

Metabolism and Elimination

The specific pathways of metabolism (biotransformation) and elimination of neuromuscular blocking drugs are summarized in Table 13-10. Of the nondepolarizing neuromuscular blockers listed, pancuronium, pipecuronium, vecuronium, atracurium, cisatracurium, mivacurium, and rapacuronium (ORG 9487) are the only ones that are metabolized or degraded. Nearly all nondepolarizing neuromuscular blocker molecules contain ester linkages, acetyl ester groups, and hydroxyl or methoxy groups. These substitutions, especially the quaternary nitrogen groups, confer a high degree of water solubility with only slight lipid solubility. The hydrophilic nature of relaxant molecules enables easy elimination in urine by glomerular filtration with no tubular resorption or secretion. Therefore, all nondepolarizing neuromuscular blockers show elimination of the parent molecule in urine as a basic route of elimination. Nondepolarizing neuromuscular blockers with a long duration of action are eliminated predominantly in urine and thus have a clearance rate limited by glomerular filtration (1 to 2 mL/kg/min).

Table 13-10 -- Metabolism and elimination of neuromuscular blocking drugs

			Elimination		
Drug	**Duration**	**Metabolism (%)**	***Kidney (%)***	***Liver (%)***	**Metabolites**
Succinylcholine	Ultrashort	Butyrylcholinesterase (98%–99%)	<2%	None	Monoester (succinylmonocholine) and choline. The monoester is metabolized much more slowly than succinylcholine is
430A	Ultrashort	Cysteine (fast) and ester hydrolysis (slow)	?	?	Inactive cysteine adduction product, chloroformate monoester and alcohol (see Fig. 13-10)
Mivacurium	Short	Butyrylcholinesterase (95%–99%)	<5%	None	Monoester and quaternary alcohol. The metabolites are inactive. They are

			Elimination		
Drug	**Duration**	**Metabolism (%)**	***Kidney (%)***	***Liver (%)***	**Metabolites**
					most likely not themselves metabolized any further (see Fig. 13-22)
			(Metabolites eliminated in urine and bile)		
Rapacuronium (ORG 9487)	Short	To 3-desacetyl metabolite	20%	Unknown	The 3-OH derivative, ORG 9488, is two to three times more potent than the parent compound and has a longer half-life
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60%–90%)	10%–40%	None	Laudanosine, acrylates, alcohols, and acids (see Fig. 13-23). Although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible
			(Metabolites eliminated in urine and bile)		
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates. Ester hydrolysis of the quaternary monoacrylate occurs secondarily (see Fig. 13-23). Because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are 5 to 10 times lower than in the case

			Elimination		
Drug	**Duration**	**Metabolism (%)**	***Kidney (%)***	***Liver (%)***	**Metabolites**
					of atracurium, thus making this a nonissue in practice
Vecuronium	Intermediate	Liver (30%–40%)	40%–50%	50%–60%	The 3-OH metabolite accumulates, particularly in renal failure. It has about 80% the potency of vecuronium and may be responsible for delayed recovery in ICU patients (see Fig. 13-21)
			(Metabolites excreted in urine and bile)		
Rocuronium	Intermediate	None	<10%	>70%	None
Pancuronium	Long	Liver (10%–20%)	85%	15%	The 3-OH metabolite may accumulate, particularly in renal failure. It is about two thirds as potent as the parent compound
d-Tubocurarine	Long	None	80% (?)	20%	None
Pipecuronium	Long	Approximately 10%	>90% (?)	<10%	The 3-OH metabolite is produced in small quantities (≈5%)
Metocurine	Long	None	>98%	<2%	None
Doxacurium	Long	None	>90% (?)	<10%	None
Alcuronium	Long	None	80%–90% (?)	10%–20%	None
Gallamine	Long	None	100%	0%	None

Steroidal Compounds

Long-Acting Neuromuscular Blockers

Pancuronium is cleared largely by the kidney.[290] Hepatic uptake of pancuronium is limited.[291] A small amount (15% to 20%) is deacetylated at the 3-position in the liver,[27][292][293] but such deacetylation makes a minimal contribution to its total clearance. Deacetylation also occurs at the 17-position, but to such a small extent that it is clinically irrelevant. The metabolites have been individually studied in anesthetized humans.[253] The 3-OH metabolite is the most potent of the three (approximately half the potency of pancuronium) and the only one present in detectable concentrations in plasma. This metabolite has pharmacokinetics and duration of action similar to those of pancuronium.[253] The 3-OH metabolite is also most probably excreted largely by the kidney.[253] The parent compound and the 3-OH metabolite are cleared in small amounts through a minor liver pathway.[292] Total clearance is delayed, and the duration of action is significantly lengthened by severe disorders of renal or hepatic function.[233][294][295][296][297]

Pipecuronium undergoes very little metabolism. Only a very small amount of the drug (5%) may be deacetylated at the 3-position. The major excretory pathway is the kidney, with the liver possibly being a minor secondary pathway. Excretion is delayed, clearance is decreased, and the elimination half-life is lengthened in the presence of major disorders of renal or hepatic function.[293][298][299]

Intermediate-Acting Neuromuscular Blockers

Vecuronium, the 2-desmethyl derivative of pancuronium, is more lipid soluble than pancuronium because of absence of the quaternizing methyl group at the 2-position. It undergoes two to three times more metabolism than pancuronium does. Vecuronium is taken up into the liver by a carrier-mediated transport system[291][300] and is deacetylated at the 3-position by liver microsomes (Fig. 13-21).[301] About 12% of vecuronium clearance is by conversion to 3-desacetylvecuronium,[302] and about 30% to 40% is cleared in bile as the parent compound.[231][303] Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (up to 25%) renal excretion, and this combined elimination gives it a clearance of 3 to 6 mL/kg/min.[302][303][304]

Figure 13-21 Metabolism of vecuronium as it occurs in the liver. About 30% to 40% of an injected dose is deacetylated at the 3- and 17-positions. The major metabolite is 3-OH vecuronium *(red arrow)*. The metabolites are excreted in urine and bile. The 3-OH metabolite is nearly as potent as the parent compound and is probably cleared from blood at a rate slightly slower than that of vecuronium. *(Redrawn from Agoston S, Seyr M, Khuenl-Brady KS, et al: Use of neuromuscular blocking agents in the intensive care unit. Anesthesiol Clin North Am 11:345, 1993.)*

The principal metabolite of vecuronium, 3-desacetylvecuronium, is a potent (≈80% of vecuronium) neuromuscular blocking drug in its own right. The metabolite, though, has lower plasma clearance and a longer duration of action than vecuronium does.[302] 3-Desacetylvecuronium has a clearance of 3.5 mL/kg/min, and renal clearance accounts for approximately a sixth of its elimination.[302] In patients in the ICU who have renal failure, 3-desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade.[305]

Other putative metabolites are 17-desacetylvecuronium and 3,17-bisdesacetylvecuronium, neither of which occurs in clinically significant amounts.[27]

Rocuronium is eliminated primarily by the liver,[306][307] with a small fraction (≈10%) eliminated in urine.[308] It is taken up into the liver by a carrier-mediated active transport system.[309][310] The putative metabolite 17-desacetylrocuronium has not been detected in significant quantities.

Short-Acting Neuromuscular Blockers

Rapacuronium has a clearance of between 8 and 11 mL/kg/min.[219][311] It probably undergoes metabolism to its 3-desacetyl derivative (ORG 9488), which contributes significantly to its neuromuscular blocking effect.[311] The metabolite (ORG 9488) is more potent and shows considerably slower elimination than does the parent compound. Accumulation of the metabolite may be the reason for slower recovery after successive doses of rapacuronium.[311]

Benzylisoquinolinium Compounds

Short-Acting Neuromuscular Blockers

Mivacurium is hydrolyzed in plasma by butyryl-cholinesterase to monoester and the amino alcohol (Fig. 13-22).[10][312] These compounds are excreted in urine and bile.[313] The metabolites are positively charged, thus making central nervous system (CNS) entry unlikely. They show less than 1/100 the neuromuscular blocking activity of the parent compound. They do not affect the autonomic nervous system.[313] Less than 5% is excreted as the parent compound in urine.

Figure 13-22 Metabolism of mivacurium by butyrylcholinesterase. The reaction occurs at about 70% to 88% of the rate of succinylcholine in vitro. The metabolites are inactive and carry positive charges, thus suggesting minimal central nervous system entry.
(Redrawn from Savarese JJ, Ali HH, Basta SJ, et al: The clinical neuromuscular pharmacology of mivacurium chloride [BW B1090U]. A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723–732, 1988.)

Mivacurium consists of three stereoisomers, and clearance of the two most pharmacologically active isomers, the *cis-trans* and *trans-trans* isomers, is approximately 100 and 50 to 70 mL/kg/min, respectively.[171][172][314] These two isomers have elimination half-lives of 2 to 3 minutes.[171] The third stereoisomer, the *cis-cis* isomer, is present as only 4% to 8% of the mivacurium mixture and has less than 10% of the neuromuscular blocking potency of the other two isomers.[171] Consequently, even though it has a much longer elimination half-life (55 minutes) and lower clearance (≈4 mL/kg/min) than the two other isomers, it does not contribute significantly to the duration of action of mivacurium.[171] This rapid enzymatic clearance of mivacurium accounts for its short duration.[10][171] Mivacurium has a duration of action much shorter than that of vecuronium and atracurium but about twice that of succinylcholine.[315]

When butyrylcholinesterase activity is severely deficient, such as in rare patients (1/3000) who are homozygotes with genetically atypical enzyme, the duration of action of mivacurium is prolonged for up to several hours.[316][317][318][319][320]

Intermediate-Acting Neuromuscular Blockers

Theoretically, atracurium is metabolized through two pathways (see Fig 13-23).[321] The drug undergoes Hofmann elimination and ester hydrolysis by nonspecific esterases. Hofmann elimination is a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine (a tertiary amine) and a mono-quaternary acrylate.[322][323] They were thought to have no neuromuscular and little or no cardiovascular activity of clinical relevance.[322][323] Under the proper chemical conditions, these breakdown products may actually be used to synthesize the parent compound.

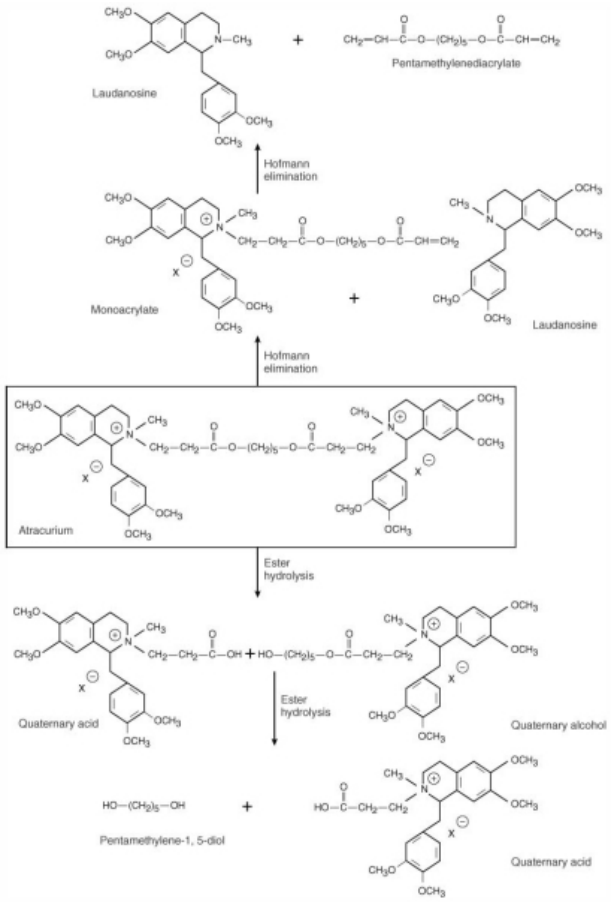

Figure 13-23 Degradation pathways of atracurium. The major metabolite, laudanosine, is excreted in urine and bile. Laudanosine is a tertiary amine that may enter the central nervous system. Less than 10% of atracurium is excreted as the parent compound.
(Redrawn from Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate [BW 33A]: A new non-depolarizing muscle relaxant. Anesth Analg 61:723–729, 1982.)

Because it undergoes Hofmann elimination, atracurium is relatively stable at pH 3.0 and 4°C and becomes unstable when injected into the bloodstream. Early observations of breakdown of the drug in buffer and plasma showed faster degradation in plasma, thus suggesting possible enzymatic hydrolysis of the ester groups.[324] Further evidence suggests that this second pathway, ester hydrolysis, may be of more importance than was originally realized in the breakdown of atracurium.[325] Through the use of pharmacokinetic analysis, Fisher and associates[326] concluded that a significant amount of clearance of atracurium may be accomplished by routes other than ester hydrolysis and Hofmann elimination. Atracurium's metabolism is complicated and may not be completely resolved.[326][327]

Laudanosine, a metabolite of atracurium, has CNS-stimulating properties. Unlike atracurium, laudanosine is dependent on the liver and kidney for elimination and has a long elimination half-life.[328][329] Laudanosine concentrations are elevated in patients with liver disease[330] and those who have received atracurium for many hours in an ICU.[331] Laudanosine freely crosses the blood-brain barrier.[328] Beemer and coworkers[332] found that patients awakened at a 20% higher arterial concentration of thiopental when atracurium had been given; such awakening was attributed to the CNS stimulatory effect of laudanosine. These relatively low concentrations of laudanosine, however, did not influence animal models of epilepsy[333] or lidocaine-induced seizures.[334] In the ICU, blood levels of laudanosine can be as high as 5.0 to 6.0 µg/mL.[331] Though not known in humans, the seizure threshold in animals ranges from 5.0 µg/mL in rabbits[335] to 17 µg/mL in dogs.[336] Thus, adverse effects are unlikely to occur with atracurium use in the operating room or the ICU. Laudanosine also has cardiovascular effects. In dogs, hypotension occurs at a blood concentration of about 6 µg/mL,[328][336] a level higher than usually found in patients in the ICU. However, there is one case report of a patient who had severe hypotension and bradycardia while receiving atracurium, which resolved only when vecuronium was substituted.[337] Laudanosine enhances stimulation-evoked release of norepinephrine,[338][339] a characteristic that may also partly account for its CNS-stimulating effect.

Atracurium is a mixture of 10 optical isomers. Cisatracurium is the 1R *cis*-1'R *cis* isomer of atracurium.[167] Like atracurium, it is metabolized by Hofmann elimination to laudanosine and a monoquaternary alcohol metabolite.[340][341][342] There is no ester hydrolysis of the parent molecule.[340] Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg/min.[343] Twenty-three percent of the drug is cleared through organ-dependent means, with renal elimination accounting for 16% of this total.[342] Because cisatracurium is about four to five times as potent as atracurium, about five times less laudanosine is produced, and accumulation of this metabolite is not thought to be of any consequence in clinical practice.

Long-Acting Neuromuscular Blockers

dTc does not undergo active metabolism. The kidney is the major pathway of elimination, with approximately 50% of a dose being eliminated through renal pathways. The liver is probably a secondary route of elimination. The drug is not indicated for use in patients with either renal[234] or hepatic[344] failure because more suitable agents are available.

Metocurine is excreted only by the kidney. It has no alternative biliary pathway, and no metabolism occurs in the liver.[345]

Doxacurium is not metabolized in humans. The drug is excreted in urine and bile as the unchanged parent molecule. Urine is the major route of elimination, with bile being a minor secondary pathway.[346]

Asymmetric Mixed-Onium Chlorofumarates (430A)

430A appears to be degraded by two chemical mechanisms, neither of which is enzymatic: (1) rapid formation of an apparently inactive cysteine adduction product, with cysteine replacing chlorine, and (2) slower hydrolysis of the ester bond adjacent to the chlorine substitution to presumably inactive hydrolysis products (see Fig. 13-10).[187]

Phenolic Ether Derivative

Gallamine is not metabolized and is excreted unchanged in the urine only. It does not have any alternative biliary excretory pathway.[347]

Diallyl Derivative of Toxiferine

Alcuronium undergoes little or no metabolism. Urine is the major excretory pathway, with a small amount of biliary clearance of unchanged drug.[190]

In summary, the long-acting neuromuscular blockers undergo minimal or no metabolism, and they are eliminated, largely unchanged, mostly by renal excretion. Hepatic pathways are less important.

Neuromuscular blockers of intermediate duration such as vecuronium, rocuronium, atracurium, and cisatracurium have clearances in the range 3 to 6 mL/kg/min because of multiple pathways of degradation, metabolism, and elimination. Atracurium is cleared two to three times more rapidly than the long-acting drugs are.[227][330][348][349][350][351] Similar clearance values have been obtained for rocuronium[352][353][354][355][356][357] and cisatracurium.[341][342][343][358][359]

The only short-acting neuromuscular blocker currently available for clinical use, mivacurium, is cleared rapidly and almost exclusively through metabolism by butyrylcholinesterase, which results in plasma clearance much greater than that of any other nondepolarizing neuromuscular blocker.[10]

Adverse Effects of Neuromuscular Blockers

Neuromuscular blocking drugs seem to play a predominant role in the occurrence of adverse reactions during anesthesia. The Committee on Safety of Medicines in the United Kingdom reported that 10.8% (218 of 2014) of adverse drug reactions and 7.3% of deaths (21 of 286) were attributable to the neuromuscular blocking drugs.[360]

Autonomic Effects

Neuromuscular blocking drugs interact with nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junction.

Dose-response ratios comparing the neuromuscular blocking potency of neuromuscular blockers (ED_{95}) with their potencies in blocking vagal (parasympathetic) or sympathetic ganglionic transmission (ED_{50}) can be constructed (Table 13-11). These ratios are termed the autonomic margin of safety of the relaxant in question. The higher the dose ratio, the lower the likelihood or the greater the safety ratio for the occurrence of the particular autonomic effect. The side effect is absent (none) in clinical practice if the safety ratio is greater than 5. The side effect is weak or slight if the safety ratio is 3 or 4, moderate if 2 or 3, and strong or prominent if the ratio is 1 or less.

Table 13-11 -- Approximate autonomic margins of safety of nondepolarizing neuromuscular blockers*

Drugs	Vagus†	Sympathetic Ganglia†	Histamine Release‡
Benzylisoquinolinium Compounds			
Mivacurium	>50	>100	3.0
Atracurium	16	40	2.5
Cisatracurium	>50	>50	None
Doxacurium	>50	>100	>4.0
d-Tubocurarine	0.6	2.0	0.6
Metocurine	3.0	16.0	2.0
Steroidal Compounds			
Rapacuronium	2.0–3.0	? 5–20	? 3.0
Vecuronium	20	>250	None
Rocuronium	3.0–5.0	>10	None
Pancuronium	3.0	>250	None
Pipecuronium	25	>200	None
Others			
Alcuronium	3.0	4.0	None
Gallamine	0.6	>100	None

* Definition: number of multiples of the ED_{95} for neuromuscular blockade required to produce the autonomic side effect (ED_{50}).

† In the cat.

‡ In human subjects.

These autonomic responses are not reduced by slower injection of the relaxant. They are dose related and are additive over time if divided doses are given. If identical to the original dose, subsequent doses will produce a similar response; that is, no tachyphylaxis will occur. Such is not the case when the side effect of histamine release is in question. Cardiovascular responses secondary to histamine release are decreased by slowing the injection rate, and the response undergoes rapid tachyphylaxis. The autonomic effects of neuromuscular blocking drugs are summarized in Table 13-12.

Table 13-12 -- Clinical autonomic effects of neuromuscular blocking drugs

Drug Type	Autonomic Ganglia	Cardiac Muscarinic Receptors	Histamine Release
Depolarizing Substance			
Succinylcholine	Stimulates	Stimulates	Slight
Benzylisoquinolinium Compounds			
Mivacurium	None	None	Slight
Atracurium	None	None	Slight
Cisatracurium	None	None	None
Doxacurium	None	None	None
d-Tubocurarine	Blocks	None	Moderate
Metocurine	Blocks weakly	None	Slight
Steroidal Compounds			
Rapacuronium*	? None	Blocks moderately	? Slight
Vecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Pancuronium	None	Blocks moderately	None
Pipecuronium	None	None	None
Others			
Alcuronium	Blocks weakly	Blocks weakly	None
Gallamine	None	Blocks strongly	None

* Has not been extensively studied; may also block calcium channels.

Histamine Release

Quaternary ammonium compounds such as neuromuscular blockers are generally weak histamine-releasing substances relative to tertiary amines such as morphine. Nevertheless, when large doses of certain neuromuscular blockers are administered rapidly, erythema of the face, neck, and upper part of the torso may develop, as well as a brief decrease in arterial pressure and a slight to moderate increase in heart rate. Bronchospasm in this setting

is very rare. The clinical effects of histamine are seen when plasma concentrations increase 200% to 300% above baseline values and involve chemical displacement of the contents of mast cell granules containing histamine, prostaglandin, and possibly other vasoactive substances.[361] The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process.[361]

The side effect of histamine release is most often noted after administration of the benzylisoquinolinium class of muscle relaxants, although it has been reported with steroidal relaxants of low potency. The effect is usually of short duration (1 to 5 minutes), is dose related, and is clinically insignificant in healthy patients. Hatano and colleagues[362] showed that the hypotensive cardiovascular response to 0.6 mg/kg dTc in humans is prevented not only by antihistamines but also by nonsteroidal anti-inflammatory drugs (e.g., aspirin). These investigators concluded that the final step in dTc-induced hypotension is modulated by prostaglandins that are vasodilators.[362] The side effect may be reduced considerably by a slower injection rate. It is also attenuated by prophylaxis with combinations of H_1- and H_2-blockers.[363] If a minor degree of histamine release such as just described occurs after an initial dose of neuromuscular blocker, subsequent doses will generally cause no response at all, as long as they are not larger than the original dose. This observation is clinical evidence of tachyphylaxis, an important characteristic of histamine release. A much more significant degree of histamine release occurs during anaphylactic or anaphylactoid reactions, but these reactions are very rare.

Clinical Cardiovascular Manifestations of Autonomic Mechanisms

Hypotension

The hypotension seen with atracurium and mivacurium is due to histamine release. dTc causes hypotension through histamine release and ganglion blockade.[364][365][366][367] More than any other neuromuscular blocker, the ganglion-blocking and histamine-releasing effects of dTc occur closer to the dose required to achieve neuromuscular blockade.[219][368] Dowdy and coworkers[369] proposed that hypotension is not caused by dTc itself but by the preservative in its formulation. However, in anesthetized patients, Stoelting[370][371] disproved this theory. The safety margin for histamine release is about three times greater for atracurium and mivacurium and two times greater for metocurine than for dTc.[215][361][362][367][372] Rapid administration of atracurium in doses greater than 0.4 mg/kg and mivacurium in doses greater than 0.15 mg/kg has been associated with transient hypotension from histamine release (Fig. 13-24).

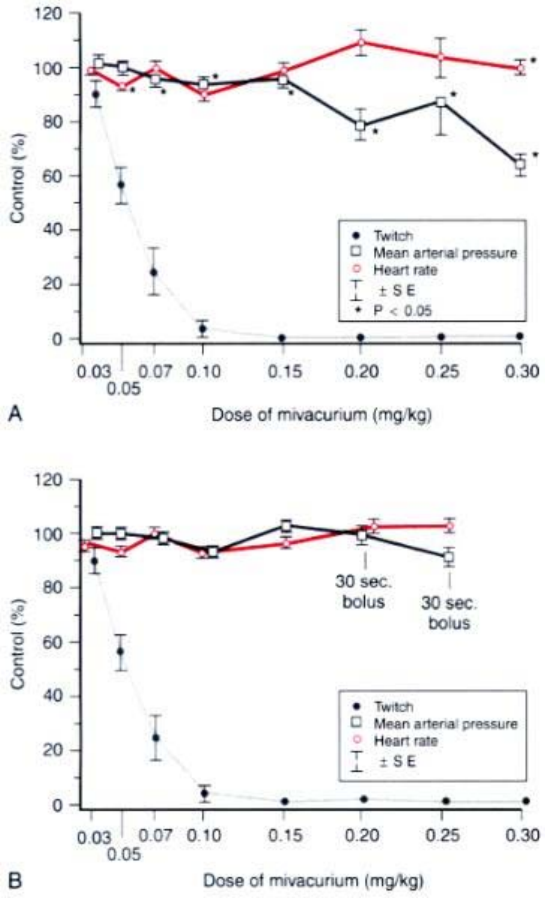

Figure 13-24 Dose response to mivacurium in patients under nitrous oxide-oxygen-opioid anesthesia. Maximum changes at each dose are shown ($n = 9$ subjects per group). **A,** With fast injection, a 15% to 20% decrease in arterial pressure occurred at2.5 to 3 × ED_{95} (0.20 to 0.25 mg/kg). **B,** The changes were less than 10% when slower injection (30 seconds) was performed.
(Redrawn from Savarese JJ, Ali HH, Basta SJ, et al: The cardiovascular effects of mivacurium chloride [BW B1090U] in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 70:386–394, 1989.)

Tachycardia

Pancuronium causes a moderate increase in heart rate and, to a lesser extent, cardiac output, with little or no change in systemic vascular resistance.[373][374] Pancuronium-induced tachycardia has been attributed to (1) a vagolytic action,[373][375] probably as a result of inhibition of M_2 receptors,[376] and (2) sympathetic stimulation involving both direct (blockade of neuronal uptake of norepinephrine) and indirect (release of norepinephrine from adrenergic nerve endings) mechanisms.[377][378][379][380] Vercruysse and associates[381] suggested that both gallamine and pancuronium augment the release of norepinephrine in vascular tissues under vagal control. In studies in humans, Roizen and colleagues[382] surprisingly found a decrease in plasma norepinephrine levels after the administration of either pancuronium or atropine. They postulated that the increase in heart rate or rate-pressure product occurs because pancuronium (or atropine) acts through baroreceptors to

reduce sympathetic outflow.[382] More specifically, the vagolytic effect of pancuronium increases the heart rate and, hence, blood pressure and cardiac output, which in turn influence the baroreceptors to decrease sympathetic tone. Support for this concept is provided by the fact that previous administration of atropine will attenuate or eliminate the cardiovascular effects of pancuronium.[373] Gallamine increases the heart rate by both a vagolytic effect[375][383] and sympathetic stimulation.[384] Specifically, gallamine releases norepinephrine from adrenergic nerve endings in the heart by an unknown mechanism.[384] However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans.[385] It would not be surprising to ultimately find out that gallamine and pancuronium act by similar mechanisms. The tachycardia seen with benzylisoquinolinium compounds is due to histamine release.

Dysrhythmias

Gallamine, dTc, and succinylcholine actually reduce the incidence of epinephrine-induced dysrhythmias.[386] Possibly because of enhanced atrioventricular conduction,[387] the incidence of dysrhythmias from pancuronium appears to increase during halothane anesthesia.[373] Edwards and collaborators[388] observed a rapid tachycardia (more than 150 beats/min) that progressed to atrioventricular dissociation in two patients anesthetized with halothane who received pancuronium. The only factor common to these two patients was that both were receiving tricyclic antidepressants.

Bradycardia

Several case reports[389][390] have described severe bradycardia and even asystole after vecuronium or atracurium administration. All these cases were associated with opioid administration. Subsequent studies have indicated that vecuronium or atracurium alone does not cause bradycardia.[391] When combined with other drugs that do cause bradycardia (e.g., fentanyl), nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium allow this mechanism to occur unopposed. The moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia.

Respiratory Effects

The muscarinic cholinergic system plays an important role in regulating airway function. Five muscarinic receptors have been cloned.[392][393][394] Cloned m1, m2, m3, and m4 muscarinic receptors correspond to the pharmacologically defined M_1, M_2, M_3, and M_4 receptors, respectively.[392][394][395] Three receptors (M_1 to M_3) exist in the airways.[396][397] M_1 receptors are under sympathetic control and mediate bronchodilation.[398] M_2 receptors are located presynaptically (Fig. 13-25) at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of acetylcholine. M_3 receptors are located postsynaptically (see Fig. 13-25), and they mediate contraction of airway smooth muscles (bronchoconstriction).[398] Nondepolarizing neuromuscular blockers have different antagonistic activities at both the M_2 and M_3 receptors.[376][399][400] Blockage of M_3 muscarinic receptors on airway smooth muscle inhibits vagally induced bronchoconstriction (i.e., causes bronchodilation),[399] whereas blockage of M_2 receptors results in increased release of acetylcholine that will act on M_3 receptors and cause bronchoconstriction. The affinity of rapacuronium to block M_2

receptors is 15 times higher than its affinity to block M_3 receptors,[400] which would explain the high incidence (>9%)[186] of severe bronchospasm[181][182][183][184] seen with this drug that resulted in its withdrawal from the market.

Figure 13-25 Muscarinic (M_3) receptors are located postsynaptically on airway smooth muscle. Acetylcholine (ACh) stimulates M_3 receptors to cause contraction. M_2 muscarinic receptors are located presynaptically at the postganglionic parasympathetic nerve endings, and they function in a negative-feedback mechanism to limit the release of acetylcholine.

Administration of benzylisoquinolinium neuromuscular blocking drugs (with the exception of cisatracurium and doxacurium) is associated with histamine release that may result in an increase in airway resistance and bronchospasm in patients with hyperactive airway disease.[401]

Allergic Reactions

The frequency of life-threatening anaphylactic (immune mediated) or anaphylactoid reactions occurring during anesthesia has been estimated at between 1 in 1000 and 1 in 25,000 anesthetics with an approximately 5% mortality rate.[402][403][404][405] Neuromuscular blocking drugs (especially succinylcholine) are the triggering agents in over 50% of these reactions.[360][406] Anaphylactic reactions are mediated through immune responses involving IgE antibodies fixed to mast cells. Anaphylactoid reactions are not immune mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals.

Neuromuscular blocking drugs contain two quaternary ammonium ions, which are the epitopes commonly recognized by specific IgE.[407] Cross-reactivity has been reported between neuromuscular blocking drugs and food, cosmetics, disinfectants, and industrial materials.[407] Cross-reactivity is seen in more than 60% of patients with a history of anaphylaxis to a neuromuscular blocking drug.[408]

Steroidal compounds (e.g., rocuronium, vecuronium, pancuronium, or pipecuronium) lack significant histamine release.[367][409] Rocuronium at doses of$4 \times ED_{95}$ (1.2 mg/kg) cause no significant histamine release.[410] Nevertheless, Laxenaire and Mertes[411] have reported a 29.2% (98/336 cases) incidence of anaphylaxis to rocuronium over a 2-year period in France. Rose and Fisher[412] classified rocuronium (and atracurium) as intermediate in risk for causing allergic reactions. They also noted that the increased number of reports of anaphylaxis with rocuronium is in the line with the market share.[412] Watkins[413] stated "The much higher incidence of rocuronium reactions reported in France is currently inexplicable and is likely to remain so if investigators continue to seek a purely antibody-mediated response as an explanation of all anaphylactoid reaction presentations." Currently, there are no standards against which diagnostic tests (skin prick test, intradermal test, or IgE testing) are performed. For instance, Laxenaire and Mertes[411] used a 1:10 dilution of rocuronium for intradermal skin testing, whereas Rose and Fisher[412] used a 1:1000 dilution. Levy and colleagues[414] showed that rocuronium in a 1:10 dilution can produce

false-positive results in intradermal testing and suggested that rocuronium be diluted at least 100-fold to prevent false-positive skin tests. Levy and coworkers[414] also found that both rocuronium and cisatracurium at high concentrations ($\geq 10^{-4}$ M) are capable of producing a wheal-and-flare response to intradermal testing associated with mild to moderate mast cell degranulation in the cisatracurium group only.

All neuromuscular blocking drugs can cause noncompetitive inhibition of histamine-*N*-methyltransferase, but concentrations required for inhibition far exceed those that would be used clinically, except for vecuronium, in which the effect becomes manifested at 0.1 to 0.2 mg/kg.[415][416] This could explain the occurrence of occasional severe bronchospasm in patients after receiving vecuronium.[417][418][419]

The goals of treatment of anaphylactic reactions are to correct arterial hypoxemia, inhibit further release of chemical mediators, and restore intravascular volume. One hundred percent oxygen and intravenous epinephrine, 10 to 20 µg/kg, should be administered immediately. Early tracheal intubation with a cuffed tracheal tube should be considered in patients with rapidly developing angioedema. Fluids (crystalloid or colloid solutions, or both) must be administered concurrently. Norepinephrine or a sympathomimetic drug (phenylephrine) may also be necessary to maintain perfusion pressure until intravascular fluid volume can be restored. Dysrhythmias should be treated. The use of antihistamines and steroids is controversial.

DRUG INTERACTIONS AND OTHER FACTORS AFFECTING RESPONSE TO NEUROMUSCULAR BLOCKERS

A drug-drug interaction is an in vivo phenomenon that occurs when the administration of one drug alters the effects or kinetics of another drug. In vitro physical or chemical incompatibilities are *not* considered drug interactions.[420]

Mechanisms of Drug Interactions

Pharmacokinetic interactions are interactions in which one drug alters the rate or amount of absorption, distribution, metabolism, or excretion of another drug (or any combination of these processes).

Pharmacodynamic interactions occur when the dose-response relationship of a drug is altered by the coadministration of a second drug. These interactions are generally described as being *synergistic, antagonistic,* or *additive*.

Many drugs have been shown to interact with neuromuscular blockers or their antagonists, or both, and it is beyond the scope of this chapter to review them all. The reader is referred to reviews on drug interactions for more detailed information.[420][421][422][423] Some of the more important drug interactions are discussed in the following sections.

Interactions among Nondepolarizing Neuromuscular Blockers

Mixtures of two nondepolarizing neuromuscular blockers are considered to be either (1) additive when the effect is the sum of equipotent doses of either drug given alone or (2)

synergistic when the effect of the mixture is greater than the equipotent dose of either drug. Antagonistic interactions have not been reported in this class of drugs.

Additive interactions have been demonstrated after the administration of chemically related agents such as atracurium-mivacurium,[424] atracurium-cisatracurium,[425] or various pairs of steroidal neuromuscular blockers.[179][426][427][428] On the other hand, combinations of structurally dissimilar (a steroidal with a benzylisoquinolinium) neuromuscular blockers, for example, pancuronium-dTc,[429] pancuronium-metocurine,[429] rocuronium-mivacurium,[251] rocuronium-cisatracurium,[212] and pancuronium-mivacurium,[430] produce a synergistic (potentiating) response.

The administration of two neuromuscular blockers in combination was first introduced by Lebowitz and colleagues[429] in an attempt to reduce the cardiovascular side effects of neuromuscular blockers by giving smaller doses of each drug as a combination.[429] Additional advantage (rapid onset and short duration) is noted for mivacurium-rocuronium combinations.[251] Although the precise mechanisms underlying a synergistic interaction are not known, hypotheses that have been put forward include (1) the existence of multiple binding sites at the neuromuscular junction (presynaptic and postsynaptic receptors)[431] and (2) nonequivalence of binding affinities of the two α-subunits (α_H and α_L) (see the section "Principles of Action of Neuromuscular Blockers at the Neuromuscular Junction"). Furthermore, inhibition of butyrylcholinesterase by pancuronium results in decreases plasma clearance of mivacurium and marked potentiation of neuromuscular blockade.[432]

It should be noted that the pharmacodynamic response after the use of two different nondepolarizing blockers in the course of anesthesia depends not only on the specific drugs used but also on the sequence of their administration. It has been shown that the effect of a maintenance dose of vecuronium given during recovery from an initial dose of either pipecuronium[433] or pancuronium[434][435] is dependent on the neuromuscular blocker that was used initially. Approximately three half-lives will be required for a clinical changeover (so that 95% of the first drug has been cleared) and for the duration of block to begin to take on the characteristics of the second drug. Smith and White[433] noted that the mean duration of a maintenance dose of vecuronium was significantly longer after pipecuronium (40 minutes) than after vecuronium (29 minutes) and was similar to that of pipecuronium after pipecuronium (49 minutes). After pipecuronium, they detected clinically significant prolongation after four maintenance doses of vecuronium.[433] After pancuronium, it has been reported that recovery from the first two maintenance doses of vecuronium is prolonged; however, this effect becomes negligible by the third dose.[434] Similarly, Naguib and coworkers[424] noted that the mean duration of the first maintenance dose of mivacurium to 10% recovery of the first twitch was significantly greater after atracurium (25 minutes) than after mivacurium (14.2 minutes). However, the duration of the second maintenance dose of mivacurium after atracurium (18.3 minutes) was similar to that of mivacurium after mivacurium (14.6 minutes).

The apparent prolongation of action of the first maintenance dose of mivacurium administered after atracurium[424] and those reported with vecuronium after pancuronium[434][435] or pipecuronium[433] is not related to synergism. Combinations of atracurium and mivacurium[424] and combinations of vecuronium and pancuronium or

pipecuronium[179][426] are simply additive. However, this prolongation in duration of action could be attributed to the relative concentrations of these drugs at the receptor site. Because most receptors remain occupied by the drug administered initially, the clinical profile depends on the kinetics/dynamics of the drug administered first rather than on that of the second (maintenance) drug. However, with further incremental doses of the second drug, a progressively larger proportion of the receptors are occupied by the second drug, and the clinical profile of that drug becomes evident.

Interaction between Succinylcholine and Nondepolarizing Neuromuscular Blockers

The interaction between succinylcholine and nondepolarizing neuromuscular blockers depends on the order of administration and the doses used.[155][436][437][438] Administration of small doses of different nondepolarizing neuromuscular blockers before succinylcholine to prevent fasciculations has an antagonistic effect on development of the subsequent depolarizing block produced by succinylcholine.[63][155] Therefore, it is recommended that the dose of succinylcholine be increased after the administration of a defasciculating dose of a nondepolarizing neuromuscular blocker.[63][439]

Studies on the effects of administration of succinylcholine before nondepolarizing neuromuscular blockers have produced conflicting results. Several investigators reported potentiation of the effects of dTc,[440] pancuronium,[437] and vecuronium and atracurium[438][441] by previous administration of succinylcholine. In contrast, others noted the opposite for dTc[436] or found no significant influence of succinylcholine on subsequent administration of pancuronium, doxacurium, pipecuronium, rocuronium, or mivacurium.[155][442][443][444][445]

Inhaled Anesthetics

Deep anesthesia with potent volatile anesthetics (in the absence of neuromuscular blockade) may cause a slight reduction in neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function such as tetanus and TOF responses.[446] Inhaled anesthetics also potentiate the neuromuscular blocking effect of nondepolarizing neuromuscular blockers. This potentiation results mainly in a decrease in the dosage requirement of the neuromuscular blocker and prolongation of both the duration of action of the relaxant and recovery from neuromuscular blockade.[447][448] The magnitude of potentiation depends on several factors, including the duration of anesthesia,[446][449][450][451][452] the specific inhaled anesthetic,[196][453] and the concentration used.[454] The rank of order of potentiation is desflurane > sevoflurane > isoflurane > halothane > nitrous oxide-barbiturate-opioid or propofol anesthesia (Fig. 13-26).[455][456][457][458]

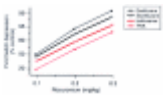

Figure 13-26 Cumulative dose-response curves for rocuronium-induced neuromuscular block during 1.5 MAC anesthesia with desflurane, sevoflurane, isoflurane, and total intravenous anesthesia.
(Redrawn from Wulf H, Ledowski T, Linstedt U, et al: Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anesthesia. Can J Anaesth 45:526–532, 1998.)

The more intense clinical muscle-relaxing effect produced by less potent anesthetics is mainly caused by their larger aqueous concentrations.[459] Desflurane and sevoflurane have low blood/gas and tissue/gas solubility, so equilibration between the end-tidal concentration and the neuromuscular junction is reached more rapidly with these agents than with other inhaled anesthetics.[460][461]

The interaction between volatile anesthetics and neuromuscular blockers is a pharmacodynamic (and not a pharmacokinetic) interaction.[247][448] Proposed mechanisms include (1) a central effect on α-motor neurons and interneuron synapses,[462](2) inhibition of the postsynaptic nAChR,[463][464][465] and (3) augmentation of the antagonist affinity at the receptor site.[459]

Antibiotics

Most antibiotics can cause neuromuscular blockade in the absence of neuromuscular blocking drugs.[466] The aminoglycoside group of antibiotics, such as polymyxins, lincomycin, and clindamycin, primarily inhibit the prejunctional release of acetylcholine and also depress postjunctional nAChR sensitivity to acetylcholine.[467][468][469] Tetracyclines, on the other hand, exhibit postjunctional activity only.[468][470][471][472] When combined with neuromuscular blockers, the aforementioned antibiotics can potentiate neuromuscular blockade.[473][474] Cephalosporins and penicillins have not been reported to potentiate neuromuscular blockade. Antagonism of neuromuscular blockade has been reported to be more difficult after the administration of aminoglycosides.[475][476] Ventilation should be controlled until the neuromuscular blockade terminates spontaneously. Calcium should not be used to hasten recovery of neuromuscular function for two reasons: the antagonism that it produces is not sustained, and it may prevent the antibacterial effect of the antibiotic. Administration of 4-aminopyridine might be of value in these situations.[474]

Temperature

Hypothermia prolongs the duration of action of nondepolarizing neuromuscular blockers.[477][478][479] The force of contraction of the adductor pollicis decreases by 10% to 16% per degree centigrade decrease in muscle temperature below 35.2°C.[480][481] To maintain muscle temperature above 35.2°C, central temperature must be maintained at 36.0°C.[477] The recovery to 10% twitch height with 0.1 mg/kg vecuronium increases from 28 minutes at a mean central temperature of 36.4°C to 64 minutes at 34.4°C.[477]

The mechanism or mechanisms underlying this prolongation may be pharmacodynamic, pharmacokinetic, or both[479] and include diminished renal and hepatic excretion, changing drug volumes of distribution, altered local diffusion receptor affinity, changes in pH at the neuromuscular junction, and the net effect of cooling on the various components of neuromuscular transmission.[477][482][483][484][485] Hypothermia decreases plasma clearance and prolongs the duration of action of rocuronium and vecuronium.[479][486] Temperature-related differences in the pharmacodynamics of vecuronium have been reported. The k_{e0}

decreased (0.023/min/°C) with lower temperature, thus suggesting slightly delayed equilibration of drug between the circulation and the neuromuscular junction during hypothermia.[479] The Hofmann elimination process of atracurium is slowed by a decrease in pH and especially by a decrease in temperature.[9][487] In fact, atracurium's duration of action is markedly prolonged by hypothermia.[478] For instance, the duration of action of 0.5 mg/kg atracurium is 44 minutes at 37°C and 68 minutes at 34.0°C.[478] Decreases in temperature also decrease the speed of neural conduction in humans.[488] A decrease in muscle temperature from 35°C to 23.5°C resulted in a 50% reduction in nerve conduction velocity.[488]

Changes in temperature will affect interpretation of the results of monitoring neuromuscular blockade. The duration of action of vecuronium measured in an arm cooled to a skin temperature of 27°C is prolonged, and monitoring by post-tetanic count in that arm is unreliable.[489] In the same patient, TOF responses are different if the arms are at different temperatures, and correlation of responses in the two arms becomes progressively poorer as the temperature difference between the arms increases.[490][491]

The efficacy of neostigmine is not altered by mild hypothermia.[492][493][494] Hypothermia does not change the clearance, maximum effect, or duration of action of neostigmine in volunteers.[494]

Magnesium and Calcium

Magnesium sulfate, given for the treatment of preeclampsia and eclamptic toxemia, potentiates the neuromuscular block induced by nondepolarizing neuromuscular blockers.[495][496][497][498][499][500] After a dose of 40 mg/kg magnesium sulfate, the ED_{50} of vecuronium was reduced by 25%, onset time was nearly halved, and recovery time just about doubled.[497] Neostigmine-induced recovery is also attenuated in patients treated with magnesium.[498][501] The mechanisms underlying the enhancement of nondepolarizing blockade by magnesium probably involve both prejunctional and postjunctional effects. High magnesium concentrations inhibit calcium channels at presynaptic nerve terminals that trigger the release of acetylcholine.[17] Furthermore, magnesium ions have an inhibitory effect on postjunctional potentials and cause a decrease in muscle fiber membrane excitability.[502] In patients receiving magnesium, the dose of nondepolarizing neuromuscular blocker must be reduced and carefully titrated by a nerve stimulator to ensure adequate recovery of neuromuscular function at the end of surgery.

The interaction of magnesium with succinylcholine is controversial. Initial studies suggested potentiation of depolarizing blockade[503] or no significant effect.[504] However, one study suggests that magnesium may antagonize the block produced by succinylcholine.[505]

Calcium triggers acetylcholine release from the motor nerve terminal and enhances excitation-contraction coupling in muscle.[17] Increasing calcium concentrations decreased the sensitivity to dTc and pancuronium in a muscle-nerve model.[506] In hyperparathyroidism, hypercalcemia is associated with decreased sensitivity to atracurium and a shortened time course of neuromuscular blockade.[507]

Lithium

Lithium remains the drug of choice for the treatment of bipolar affective disorder (manic-depressive illness). The lithium ion resembles sodium, potassium, magnesium, and calcium ions and may therefore affect the distribution and kinetics of all these electrolytes.[508][509] Lithium enters cells through sodium channels and tends to accumulate within cells.

Lithium, by activation of potassium channels, inhibits neuromuscular transmission presynaptically and muscular contraction postsynaptically.[510] The combination of lithium and pipecuronium resulted in a synergistic inhibition of neuromuscular transmission, whereas the combination of lithium and succinylcholine resulted in an additive inhibition.[510][511] Prolongation of neuromuscular blockade was reported in patients receiving lithium carbonate and both depolarizing[512][513] and nondepolarizing neuromuscular blockers.[513][514][515][516] Only one report did not demonstrate prolongation of recovery from succinylcholine in patients receiving lithium.[517] In patients undergoing surgery who are stabilized on lithium therapy, neuromuscular blockers should be administered in incremental and reduced doses and titrated to the degree of block required.

Local Anesthetics and Antidysrhythmics

Local anesthetics have actions on the presynaptic, postsynaptic, and muscle membranes. In large intravenous doses, most local anesthetics block neuromuscular transmission; in smaller doses, they enhance the neuromuscular block from both nondepolarizing and depolarizing neuromuscular blockers.[518][519] The ability of neostigmine to antagonize a combined local anesthetic-neuromuscular blockade has not been studied. Procaine also inhibits butyrylcholinesterase and may augment the effects of succinylcholine and mivacurium by decreasing their hydrolysis by the enzyme.

In small intravenous doses, local anesthetics depress post-tetanic potentiation, and this depression is thought to be a neural, prejunctional effect.[520] At higher doses, local anesthetics block acetylcholine-induced muscular contractions, which suggests that local anesthetics have a stabilizing effect on the postjunctional membrane.[521] Procaine has been shown to displace calcium from the sarcolemma and thus inhibit caffeine-induced contracture of skeletal muscle.[522] Most of these mechanisms of action probably apply to all the local anesthetics.

Several drugs used for the treatment of dysrhythmias augment the block from neuromuscular blockers, particularly that of dTc.[523] Quinidine potentiates the neuromuscular block from both nondepolarizing and depolarizing neuromuscular blockers.[524] Edrophonium is ineffective in antagonizing a nondepolarizing blockade after quinidine. In clinical doses, quinidine appears to act at the prejunctional membrane as judged by its lack of effect on acetylcholine-evoked twitch.

In a rat phrenic-hemidiaphragm preparation, Salvador and coworkers[525] showed substantial potentiation of succinylcholine by diltiazem or verapamil and potentiation of pancuronium by nicardipine. These interactions were not found in humans.[526][527] Clinical reports have suggested potentiation of neuromuscular blockade with verapamil[528] and impaired reversal

of vecuronium in a patient receiving disopyramide.[529] The clinical significance of these interactions is probably minor

Antiepileptic Drugs

Anticonvulsants have a depressant action on acetylcholine release at the neuromuscular junction.[530][531][532][533] Patients receiving chronic anticonvulsant therapy demonstrated resistance to nondepolarizing muscle blockers (except mivacurium[534] and probably atracurium as well[533][535]), as evidenced by accelerated recovery from neuromuscular blockade and the need for increased doses to achieve a complete neuromuscular block.[536][537][538] Vecuronium clearance is increased twofold in patients receiving chronic carbamazepine therapy.[539] Others, however, have attributed this resistance to increased binding (decreased free fraction) of the neuromuscular blockers to α_1-acid glycoproteins or upregulation of neuromuscular acetylcholine receptors, or a combination of both mechanisms.[540] The latter could also explain the hypersensitivity seen with succinylcholine.[541] The slight prolongation of succinylcholine action in patients taking anticonvulsants has few clinical implications. On the other hand, the potential hyperkalemic response to succinylcholine in the presence of receptor upregulation is of concern.

Diuretics

In patients undergoing renal transplantation, the intensity and duration of dTc neuromuscular blockade is increased after a dose of furosemide (1 mg/kg intravenously).[542] Furosemide reduced the concentration of dTc required to achieve 50% depression of twitch tension in the indirectly stimulated rat diaphragm and intensified the neuromuscular blockade produced by dTc and succinylcholine.[543] Furosemide appears to inhibit the production of cyclic adenosine monophosphate. Breakdown of adenosine triphosphate is inhibited and results in reduced output of acetylcholine. Acetazolamide has been found to antagonize the effects of anticholinesterases in the rat phrenic-diaphragm preparation.[544] However, in one report, 1 mg/kg furosemide facilitated recovery of the evoked twitch response after pancuronium.[545] Chronic furosemide treatment had no effect on either dTc- or pancuronium-induced neuromuscular blockade.[546]

By contrast, mannitol appears to have no effect on nondepolarizing neuromuscular blockade. Furthermore, increasing urine output by the administration of mannitol or other osmotic or tubular diuretics has no effect on the rate at which dTc and presumably other neuromuscular blockers are eliminated in urine.[230] However, this lack of effect on excretion of dTc should not be surprising. Urinary excretion of all neuromuscular blockers that are long acting depends primarily on glomerular filtration. Mannitol is an osmotic diuretic that exerts its effects by altering the osmotic gradient within the proximal tubules so that water is retained within the tubules. An increase in urine volume in patients with adequate glomerular filtration therefore would not be expected to increase the excretion of neuromuscular blockers.

Other Drugs

Dantrolene (see Chapter 29), a drug used for the treatment of malignant hyperthermia, prevents Ca^{2+} release from the sarcoplasmic reticulum and blocks excitation-contraction coupling. Although it does not block neuromuscular transmission, the mechanical response to stimulation will be depressed without demonstrating any effect on the electromyogram.[547][548] The effects of nondepolarizing neuromuscular blockers are enhanced by dantrolene.[157]

Azathioprine, an immunodepressant drug used in renal transplantation, has a minor antagonistic action on muscle relaxant-induced neuromuscular blockade.[549][550]

Steroids antagonize the effects of nondepolarizing neuromuscular blockers in humans.[551][552] Animal studies have also demonstrated resistance to the effects of dTc in the presence of prednisolone, dexamethasone, betamethasone, and triamcinolone.[553][554][555] Possible mechanisms for this interaction include (1) facilitation of acetylcholine release as a result of the effect of steroids on the presynaptic motor nerve terminal[556] or (2) channel blockade of the nAChR.[557] It should be noted that endogenous steroids act noncompetitively on nAChRs.[558] Prolonged treatment—combining corticosteroids with neuromuscular blocking drugs—can result in prolonged weakness (see the section "Neuromuscular Blockers and Weakness Syndromes in the Critically Ill").

Antiestrogenic drugs such as tamoxifen appear to potentiate the effects of nondepolarizing neuromuscular blockers.[559]

RECOVERY FROM NEUROMUSCULAR BLOCKADE

In the 1970s, Ali and coauthors[560][561] described a TOF ratio of 0.60 as being indicative of adequate recovery of neuromuscular strength. As described in the section "Monitoring Neuromuscular Function," with a TOF ratio of 0.6 to 0.7, patients will have, on average, a vital capacity of 55 mL/kg, a negative inspiratory force of 70 cm H_2O, and a peak expiratory flow of 95% of control values. This degree of recovery should allow for normal respiratory function[57] and maintenance of a patent airway. More recently, though, a TOF ratio of 0.70 in unanesthetized volunteers has been associated with difficulty speaking and swallowing, weakness of the facial musculature, visual disturbances, and an inability to sit up without assistance.[54] Administration of small doses of nondepolarizing neuromuscular blockers (one tenth of an intubating dose) as a defasciculating or precurarizing dose may cause appreciable decreases in the TOF response.[280][562] These small doses of neuromuscular blockers may be associated with general discomfort, malaise, difficulty swallowing, ptosis, and blurred vision. Recent studies in volunteers have shown that TOF ratios of 0.6 to 0.7 are associated with decreased upper esophageal tone and a decrease in coordination of the esophageal musculature during swallowing.[563][564] Fluoroscopic study of these individuals demonstrated significant pharyngeal dysfunction resulting in a fourfold to fivefold increase in the risk of aspiration. With recovery of the TOF ratio to 0.9, esophageal tone and pharyngeal coordination return toward baseline.

Residual paralysis also decreases the hypoxic ventilatory drive (Fig. 13-27).[565][566] This effect appears to be due to inhibition of the carotid body neural response to hypoxia.[567]

Vecuronium decreases carotid sinus nerve activity in response to hypoxia in a dose-related fashion, presumably through its interaction with neural nicotinic receptors.

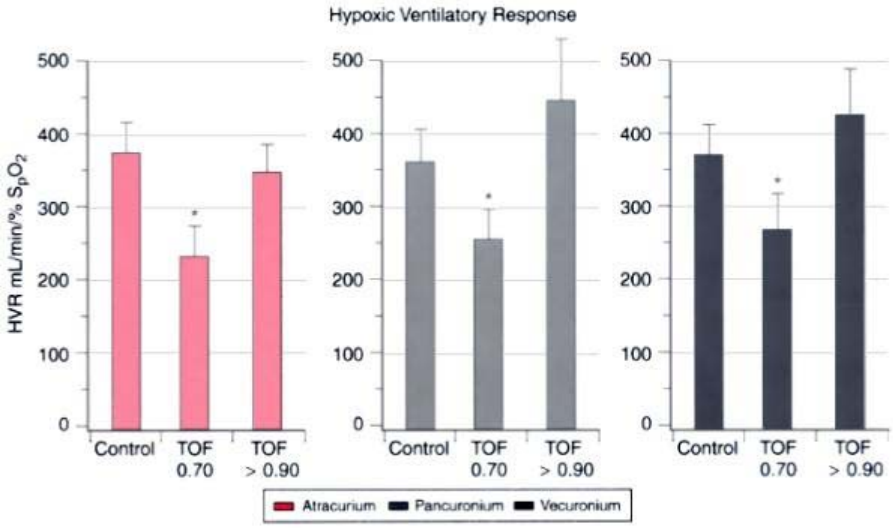

Figure 13-27 Hypoxic ventilatory response (HVR) before (control), during steady-state infusion (train-of-four [TOF] ratio = 0.07) of atracurium, pancuronium and vecuronium, and after recovery (TOF > 0.90). Data are presented as means ± SD. **P* < .01.
(Redrawn from Eriksson LI: Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? Acta Anaesthesiol Scand 40:520–523, 1996.)

After the administration of nondepolarizing neuromuscular blocking drugs, it is essential to ensure adequate return of normal neuromuscular function. Whether that degree of recovery is a TOF ratio of 0.7, 0.8, or 0.9 is an area of debate.[568] Certainly, the clinician's ability to quantify the degree of residual neuromuscular block is limited (as described in the section "Monitoring Neuromuscular Function"). Kopman and colleagues' work in volunteers demonstrated that when they could oppose their incisors to retain a tongue depressor, their TOF ratio was, on average, 0.8 and at least 0.68.[54] This test of muscle strength, however, would be of limited usefulness in an intubated patient.

Recovery from muscle relaxation caused by nondepolarizing neuromuscular blockers is dependent on several factors. Primarily, it depends on an increase in the acetylcholine concentration relative to that of the relaxant to overcome the competitive neuromuscular block. The relative increase in acetylcholine concentration depends first on the ongoing movement of relaxant from the motor end plate into the central circulation and then on its elimination from the circulating blood volume so that it is not free to move into the synaptic cleft. Ultimately, recovery depends on elimination of the neuromuscular blocker from the body. Neuromuscular blockers may be eliminated from the body through a host of mechanisms, including excretion as unchanged drug in urine, metabolism in the liver, enzymatic hydrolysis, and chemical breakdown. Although it has never been specifically examined, several manuscripts have, through their ranges of recovery parameters, described

a wide range of interpatient variability in spontaneous recovery of neuromuscular function.[569][570][571] With administration of repeated doses of a drug that relies on the kidney or the liver for its elimination from the body, plasma concentrations of the drug increase during recovery of neuromuscular function.[227][235] This increase is probably due to the fact that recovery of neuromuscular function after administration of these neuromuscular blockers occurs as the relaxant is redistributed to storage sites in the body rather than during elimination of the compound. This mechanism is in contrast to the plasma concentrations of a neuromuscular blocker such as atracurium during recovery of neuromuscular function and subsequent redosing.[227][235] In this case, plasma concentrations of the neuromuscular blocker during recovery consistently return to the same level.

Several factors in addition to coexisting disease will have an impact on the speed of spontaneous recovery of neuromuscular function. The presence of volatile anesthetics will potentiate any existing neuromuscular block and, presumably, render recovery more prolonged.[572] If the anesthesiologist observes no or minimal recovery of neuromuscular function in the presence of a volatile anesthetic, discontinuing or decreasing the concentration of inhaled anesthetic being administered should augment recovery of neuromuscular function.

As will be discussed later, acidosis, hypokalemia, hypothermia, and concomitant medications will all potentiate residual neuromuscular blockade and render pharmacologic antagonism more difficult.

Antagonism of Residual Neuromuscular Blockade

Anticholinesterases act by inhibiting the enzyme acetylcholinesterase. Acetylcholinesterase (enzyme classification 3.1.1.7) is a type B carboxylesterase. At the neuromuscular junction, it occurs in the asymmetric or A12 form, which consists of three tetramers of catalytic subunits covalently linked to a collagen-like tail.[573] Acetylcholinesterase has a powerful catalytic capacity.[29] It can catalyze 4000 molecules of acetylcholine per active site per second.[29] Nearly half of the released acetylcholine is hydrolyzed across the synaptic cleft before reaching nAChRs. The active site lies deep inside the enzyme protein.[574] For a detailed account of this enzyme, see Soreq and Seidman.[575]

The active surface of acetylcholinesterase is best viewed as having two sites: (1) the anionic site, which is concerned with binding and orienting the substrate molecule, and (2) the esteratic site, which is responsible for the hydrolytic process.[576] A second "anionic" site, known as the "peripheral" anionic site, was also proposed.[577]

Three anticholinesterases, neostigmine, edrophonium, and pyridostigmine, are used to antagonize residual neuromuscular blockade. They exert their effect primarily by increasing the concentration of acetylcholine at the motor end plate by inhibiting acetylcholinesterase. Neostigmine and pyridostigmine are oxydiaphoretic (acid transferring) inhibitors of acetylcholinesterase. Neostigmine and pyridostigmine transfer a carbamate group to the acetylcholinesterase, which forms a covalent bond at the esteratic site. Edrophonium binds to the anionic site on acetylcholinesterase by electrostatic attraction and to the esteratic subsite by hydrogen bonding.[578] In addition, anticholinesterases may also increase the

release of acetylcholine from presynaptic nerve terminals, block neural potassium channels, and have a direct agonist effect.[27] Details of the mechanisms of action of these anticholinesterases have been described in review articles.[579][580]

Major Determinants of Speed and Adequacy of Reversal

Antagonism of nondepolarizing blockade is time dependent. Reversal occurs at a rate that depends primarily on five factors: (1) the depth of block at the time of administration of the antagonist, (2) the antagonist administered, (3) the dose of antagonist, (4) the rate of spontaneous recovery from the neuromuscular blocker, and (5) the concentration of the inhaled anesthetic present during reversal.

Depth of Block

As was shown with the long-acting neuromuscular blocker pancuronium, more time is required to antagonize profound levels of block than lesser levels of block.[254][581][582] Antagonism of pancuronium blockade with 2.5 mg (about 35 µg/kg) of neostigmine shows that the relationship of reversal time to depth of blockade is hyperbolic, with a "knee" in the curve occurring at 80% to 90% twitch inhibition (Fig. 13-28). Lesser degrees of block are associated with more rapid recovery of neuromuscular function. Recovery of single-twitch height from deep levels of neuromuscular blockade requires, as demonstrated in these older studies, 15 to 30 minutes. Recovery of the TOF ratio occurs more slowly than that of a single twitch. Therefore, even more time will be required for recovery to a TOF ratio of more than 0.7 when blockade by long-acting drugs is being antagonized.

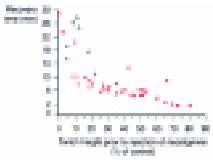

Figure 13-28 Correlation between twitch height when a bolus of neostigmine (2.5 mg) was given intravenously and the time that it took for twitch height to return to its control height. *(Redrawn from Katz RL: Clinical neuromuscular pharmacology of pancuronium. Anesthesiology 34:550–556, 1971.)*

Interestingly, a study by Bevan and coworkers[583] demonstrated that antagonism of1.5 × ED_{95} doses of vecuronium- or rocuronium-induced block occurred at the same rate regardless of the timing of administration of the 70 µg/kg neostigmine. Neostigmine shortened recovery, whether administered at 1%, 10%, or 25% spontaneous recovery, by approximately 40%. As shown in Figure 13-29, the time from administration of the neuromuscular blocker to TOF ratios of 0.7 and 0.9 was not decreased, though, because the extent of spontaneous recovery at the time of neostigmine administration increased. Recovery to TOF ratios of 0.7 and 0.9 required, on average, 25 and 30 minutes, respectively. Recommendations regarding the timing of administration of anticholinesterase remain unclear. However, because the time from administration of the anticholinesterase to full recovery is shortened by waiting for a greater degree of spontaneous recovery before administering the anticholinesterase, it would seem prudent to not administer the anticholinesterase at the earliest degrees of recovery. Kirkegaard and colleagues[584] recently demonstrated that to recover to a TOF ratio of 0.7 within 10 minutes of administering

neostigmine, three or four responses to TOF stimulation had to be present at the time of neostigmine administration. If only one response to TOF stimulation were present, recovery to a TOF ratio of 0.7 required up to 23 minutes.

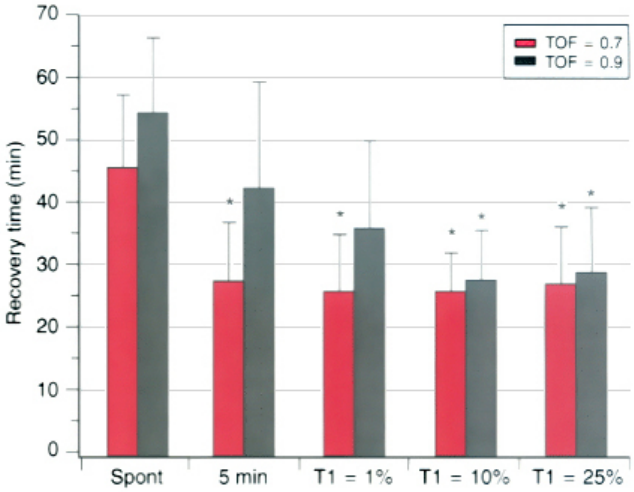

Figure 13-29 Recovery times (mean ± SD) after administration of a single dose of 0.45 mg/kg (1.5 × ED_{95}) rocuronium. In one group (Spont), spontaneous recovery is allowed. In the remaining groups, 70 µg/kg neostigmine is administered 5 minutes after rocuronium or at 1%, 10%, and 25% recovery of the first twitch (T1) from its control value. *P < 0.01 versus spontaneous recovery. Note that times to attain a train-of-four ratio of 0.9 are significantly shorter when neostigmine is administered at T1 = 10% or 25% of control tension.
(Figure constructed based on data redrawn from Bevan JC, Collins L, Fowler C, et al: Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children. Anesth Analg 89:333–339, 1999.)

The maximum antagonistic effect of neostigmine occurs in 10 minutes or less.[585][586] If adequate recovery does not occur within this time, subsequent recovery is slow and requires ongoing elimination of the neuromuscular blocker from plasma. For profound vecuronium-induced blockade in which no twitch recovery has occurred, administration of neostigmine, 70 µg/kg, produces an initial reversal that falls far short of adequate recovery.[571] Subsequent recovery is at the same rate as spontaneous recovery and is due to the decrease in plasma concentration of vecuronium as the drug is eliminated.[571][587] Administration of a second dose of neostigmine has no further effect on recovery[571] because acetylcholinesterase is already maximally inhibited.

If the block at the time of neostigmine administration is sufficiently deep that adequate recovery does not occur within 10 minutes, the time at which full recovery of neuromuscular function will occur depends on the inherent duration of action of the neuromuscular blocker.[582] With drugs that have a long duration of action, this period of inadequate neuromuscular function can be 30 to 60 minutes or longer, whereas with drugs that have an intermediate duration of action, it will be much shorter (i.e., 15 to 30 minutes).[60]

The Anticholinesterase Administered

Under conditions of moderate depth of blockade (such as two to three twitches palpable by TOF monitoring), the order of rapidity of antagonism of residual blockade by anticholinesterases is edrophonium > neostigmine > pyridostigmine.[585][588] For this reason and because of its lesser atropine requirement, edrophonium regained popularity as an antagonist during the 1980s.[585] However, Rupp and coworkers[589] found that edrophonium is not as effective as neostigmine in antagonizing profound blockade of greater than 90% twitch depression (only one twitch palpable by TOF). Although increasing the edrophonium dose from 0.5 to 1.0 mg/kg increases its efficacy, neostigmine remains capable of more complete antagonism.[589] To be equivalent to 40 µg/kg neostigmine as an antagonist of profound vecuronium blockade, 1.5 mg/kg of edrophonium has to be administered.[590]

The relative potencies of edrophonium and neostigmine differ at various intensities of blockade (Fig. 13-30).[591] Edrophonium becomes less potent with respect to neostigmine as the depth of blockade becomes more intense. In other words, the dose-response curves are not parallel and become increasingly divergent as the depth of blockade intensifies. This difference indicates that edrophonium may be less effective than neostigmine when antagonizing very deep levels of blockade.

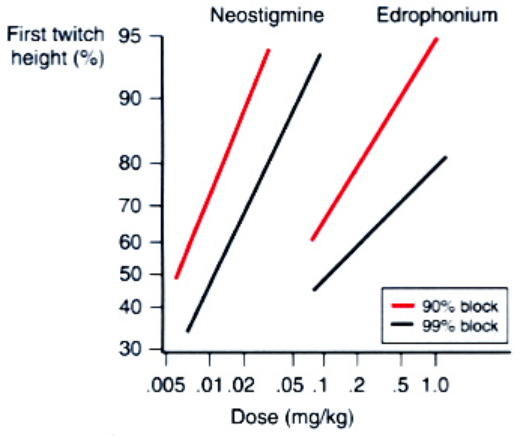

Figure 13-30 First twitch height (logit scale) versus dose (log scale) 10 minutes after administration of neostigmine and edrophonium given at either 1% (99% block) or 10% (90% block) recovery of the first twitch.
(Redrawn from Donati F, Smith CE, Bevan DR: Dose-response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 68:13–19, 1989.)

The Dose of Anticholinesterase

Larger doses of anticholinesterases should antagonize neuromuscular blockade more rapidly and more completely than smaller doses do. This relationship is true up to the point of the maximum effective dose, beyond which further amounts of anticholinesterase will not produce any further antagonism. For neostigmine, this maximum dosage is in the range 60 to 80 µg/kg[571][592]; for edrophonium, the range is 1.0 to 1.5 mg/kg.[589][590]

Donati and associates[593] studied the reversal of 90% block induced by either dTc or pancuronium to demonstrate the relationship of the dose of neostigmine to the speed of reversal. They showed that increasingly greater amounts of antagonism of neuromuscular block occurred over the course of 10 minutes as the neostigmine dosage was increased from 5 to 50 µg/kg. Even after 50 µg/kg, however, twitch had recovered to only 80% of normal strength 10 minutes after neostigmine administration.

Mixing or combining antagonists is not advisable. Neostigmine and edrophonium do not potentiate each other; in fact, their effects in combination may not even be additive.[594][595] Therefore, when inadequate reversal occurs, one should not be tempted to add a different anticholinesterase but should ensure only that the maximum dose of the original drug has been administered. Ventilation should then be supported until adequate neuromuscular function is achieved.

Rate of Spontaneous Recovery from the Neuromuscular Blocker

After administration of an anticholinesterase, two processes contribute to recovery of neuromuscular function. The first is antagonism induced by the effect of the anticholinesterase at the neuromuscular junction; the second is the natural process of decrease in the plasma concentration of the neuromuscular blocker (and hence the concentration of the neuromuscular blocker at the neuromuscular junction).[582][587] Therefore, the more rapid the elimination of the neuromuscular blocker, the faster the recovery of adequate neuromuscular function after the administration of an antagonist (Fig. 13-31).[596] A clear illustration of this principle is the difference in antagonizing a block induced by neuromuscular blockers with an intermediate versus a long duration of action. Plasma concentrations of drugs with an intermediate duration of action decrease more rapidly than do concentrations of drugs with a long duration of action,[245] and consequently recovery of neuromuscular function is more rapid.[586][594][595] The incidence of inadequate neuromuscular function in the postoperative period is less with intermediate-acting than with long-acting neuromuscular blockers.[59][60] Nevertheless, the blocks from *all* intermediate-acting muscle relaxants should be reversed with an anticholinesterase drug.[597] Because of the inability to detect subtle neuromuscular blocks clinically and persistence in the recovery room, pharmacologic reversal should be routine.[598]

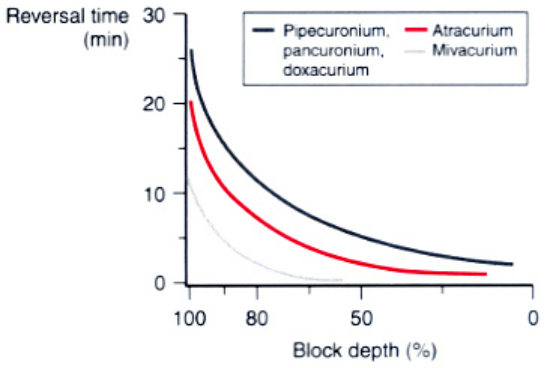

Figure 13-31 Comparative mean speed of antagonism by neostigmine of neuromuscular blockade induced by long-acting

drugs (doxacurium, pancuronium, pipecuronium), intermediate-acting drugs (atracurium and others), and the short-acting drug mivacurium. Antagonism is more rapid as processes of clearance increase (see text).
(Redrawn from Savarese JJ: Reversal of nondepolarizing blocks: More controversial than ever? Review Course Lectures, 67th Congress, Cleveland, Ohio, International Anesthesia Research Society, 1993.)

The interaction of spontaneous recovery and anticholinesterase-induced reversal of mivacurium is more complex. The rate of spontaneous recovery from mivacurium-induced blockade is more rapid than that from any other nondepolarizing neuromuscular blocker because of its rapid hydrolysis by butyrylcholinesterase. Neostigmine-induced reversal of mivacurium is similar to or faster than that of atracurium.[315][599] During profound (<3% twitch recovery) mivacurium-induced blockade, administration of neostigmine may possibly prolong recovery.[600] Neostigmine has two major effects relevant to mivacurium. First, it inhibits acetylcholinesterase at the neuromuscular junction, thereby effectively increasing the acetylcholine concentration and facilitating recovery. Second, it inhibits butyrylcholinesterase, the enzyme responsible for the metabolism of mivacurium, and slows the normally rapid decrease in plasma concentration of mivacurium.[601][602] In contrast, edrophonium is not as potent an inhibitor of butyrylcholinesterase,[601][603] and it should have little effect on the metabolism of mivacurium. Provided that there is 10% recovery of the twitch response (one twitch in the TOF), either neostigmine, 20 to 40 µg/kg, or edrophonium, 0.3 to 0.5 mg/kg, will accelerate recovery from mivacurium.[579][599][604]

It has been suggested that routine administration of an anticholinesterase may often be omitted because spontaneous recovery from mivacurium is so rapid.[605] However, this strategy may lead to inadequate recovery and postoperative weakness unless at least 20 minutes is allowed for spontaneous recovery.[599][604] As indicated earlier, administration of an anticholinesterase drug should probably be routine.[598]

Because mivacurium is metabolized by butyrylcholinesterase, recovery, in theory, may be made more rapid by the administration of exogenous human butyrylcholinesterase. Administration of purified human cholinesterase does produce some antagonism of mivacurium-induced blockade,[606] but it is ineffective in a profound block[601] and no better than edrophonium alone.[607] It may be justified to administer purified butyrylcholinesterase to patients homozygous for atypical butyrylcholinesterase who have a prolonged block,[320][608] but this therapy has yet to be adequately tested and is expensive.

Concentration of Inhaled Anesthetic

Several studies have documented that antagonism of residual blockade is actually retarded by anesthetizing concentrations of volatile anesthetics.[609][610][611][612][613] For example, Delisle and Bevan[609] showed that pancuronium reversal by neostigmine under enflurane anesthesia occurred more slowly than under nitrous oxide and intravenous anesthetics. It has even been suggested that the effect is different for different anesthetics and that sevoflurane may impede neostigmine-induced antagonism more than isoflurane does.[610] When compared with isoflurane anesthesia, the recovery variables are prolonged during desflurane or sevoflurane anesthesia.[614][615] Withdrawal of the inhaled anesthetic at the end

of surgery, with subsequent reduction of its enhancement of neuromuscular blockade, will speed pharmacologic reversal.[572]

Clinical Recommendations

When antagonizing deep levels of neuromuscular blockade (≈10% recovery or one twitch in response to TOF stimulation), larger doses of anticholinesterases should be administered and adequate time allowed for recovery of neuromuscular function. The time required for recovery to a TOF ratio of 0.7 will be approximately 60 minutes for the long-acting neuromuscular blocking drugs and 30 minutes for the intermediate-acting ones. To antagonize lesser degrees of block, smaller doses of anticholinesterases may be administered, with additional anticholinesterase given if adequate recovery has not occurred in 10 minutes.

The maximum dose of neostigmine that should be administered is 70 µg/kg. Giving too much anticholinesterase to antagonize residual neuromuscular blockade may actually render patients weaker,[570][616][617] probably because of the excess of acetylcholine at the neuromuscular junction that remains available to interact with the acetylcholine receptor.

Other Factors That May Interfere with Antagonism

It is not advisable to administer further anticholinesterase if maximal doses of edrophonium (1.5 mg/kg), neostigmine (70 µg/kg), or pyridostigmine (350 µg/kg) fail to antagonize residual blockade.[590][592] These doses inhibit acetylcholinesterase completely, and if they fail to fully antagonize residual blockade, another likely cause of the inadequate antagonism should be sought. Some of these additional potential causes of inadequate antagonism of neuromuscular blockade are described in the following sections.

Acid-Base State

Both metabolic and respiratory acidosis may augment a nondepolarizing neuromuscular blockade, but only respiratory acidosis prevents adequate antagonism.[588][618][619] The probability of achieving adequate antagonism of nondepolarizing neuromuscular blockade in the presence of significant respiratory acidosis ($PaCO_2$ greater than 50 mm Hg) is low. Therefore, if a patient hypoventilates, attempts to antagonize a residual block may fail. Administration of narcotics to relieve pain may, by producing hypoventilation, increase the likelihood of this adverse event.

Although metabolic acidosis might also be predicted to prevent antagonism by neostigmine, this theory has not been substantiated.[588][618][619] Metabolic alkalosis, but not metabolic acidosis, prevents neostigmine antagonism of dTc and pancuronium.[588][618][620] These results suggest that the extracellular hydrogen ion concentration (pH) may not be as important as changes in electrolytes and intracellular pH.

Electrolyte Imbalance

Although it has been the subject of review articles,[621] few data are available on the effect of electrolyte imbalance on antagonism of nondepolarizing neuromuscular blockade by

neostigmine. Low extracellular concentrations of potassium enhance the blockade from nondepolarizing neuromuscular blockers and diminish the ability of neostigmine to antagonize the blockade. This effect is based on the increase in end-plate transmembrane potential that results from a higher ratio of intracellular to extracellular potassium. Thus, a decrease in extracellular potassium causes hyperpolarization and produces resistance to depolarization. Patients with an imbalance in potassium may have other diseases or injuries that alter their response to neuromuscular blockers (e.g., patients with burns). Cohen[622] and Feldman[621] speculated that in chronic diseases, both intracellular and extracellular potassium is depleted with little net effect on transmembrane potential. Therefore, the response to neuromuscular blockers and their antagonists should be normal. However, muscle transmembrane potentials are changed in patients who are severely ill or bedridden for a few days.[623] In addition, severe dehydration will concentrate the neuromuscular blocker present in plasma, in effect decreasing the volume of distribution and increasing muscle relaxant activity. In an animal model of chronic hypokalemia, cats were given a diuretic without potassium supplementation for 15 days. Less pancuronium was required for neuromuscular blockade and more neostigmine for antagonism.[624] Even though the differences were small, the blockade was always antagonized completely. Assuming that this animal model approximates the clinical situation, changes in potassium appear to be of relatively minor consequence with respect to the clinical question of adequacy of reversal.

Other Factors

The calcium channel blocker verapamil will potentiate nondepolarizing neuromuscular blocking drugs and may make it difficult to achieve adequate reversal of blockade.[625][626] When attempting reversal of neuromuscular blockade in patients receiving verapamil, edrophonium may be more effective than neostigmine.[625][626] Other factors that may interfere with antagonism are hypothermia and the administration of antibiotics, particularly the aminoglycoside or polypeptide classes (see "Drug Interactions").[467][468][469][470][471][472][473][474] In the case of antibiotics, administration of an anticholinesterase may in fact deepen the blockade. Monitoring with a nerve stimulator, if aminoglycosides have been administered,[627] may give misleading results.

Side Effects of Anticholinesterases

Cardiovascular Effects

Because only the nicotinic effects of edrophonium, neostigmine, and pyridostigmine are desired, the muscarinic effects must be blocked by atropine or glycopyrrolate.[27] Atropine induces its vagolytic effect much more rapidly than glycopyrrolate does. To minimize cardiovascular changes, atropine is better suited for administration with the rapid-acting edrophonium,[27] and glycopyrrolate is better suited for administration with the slower-acting neostigmine and pyridostigmine.[628] In general, 7 to 10 µg/kg of atropine should be given with 0.5 to 1.0 mg/kg of edrophonium.[585] Atropine administration 30 seconds before edrophonium will decrease the ventricular ectopy associated with this anticholinesterase.[629] Glycopyrrolate (7 to 15 µg/kg) should be given with neostigmine (40 to 70 µg/kg). Administration of atropine with pyridostigmine will induce an initial tachycardia,[630] and giving glycopyrrolate with edrophonium may result in an initial bradycardia unless it is administered at least 1 minute earlier.[631] Dysrhythmias can occur,[631][632][633][634][635] and

anticholinesterases should be used with caution in patients with autonomic neuropathy.[632] When cardiac dysrhythmias are a concern, glycopyrrolate may be preferable to atropine,[635] and the anticholinesterases and anticholinergics should be administered over a longer period (e.g., 2 to 5 minutes) to reduce the incidence and severity of the disorders of rhythm.

Nausea and Vomiting

Reports on the effect of anticholinesterase administration on postoperative nausea and vomiting are conflicting. Neostigmine administration has been implicated as a cause of postoperative nausea and vomiting.[636][637] It has also been described as having antiemetic properties[638] and as having no impact on postoperative nausea and vomiting.[639] A meta-analysis by Tramer and Fuchs-Bader[640] looked at the results of anticholinesterase administration in over 1100 patients. They found a dose-response relationship for the incidence of nausea and vomiting after the administration of neostigmine. The highest incidence of emesis after the administration of 1.5 mg neostigmine was lower than the lowest incidence of emesis after the administration of 2.5 mg neostigmine. Discrepancies in the other studies may have been at least in part attributable to different dosing regimens. Although emesis will develop in one in three to six patients after the administration of neostigmine, the authors did not recommend letting all patients recover spontaneously because this practice introduced the risk of patients having postoperative residual paralysis. A more recent study demonstrated the hazards of not antagonizing residual neuromuscular blockade at least 2 hours after the administration of two times the ED_{95} of vecuronium, rocuronium, or atracurium.[55] Two hours after administration of these agents, 10% of 526 patients had TOF ratios less than 0.7 and 37% had TOF ratios less than 0.9.

Pharmacokinetics of Neostigmine, Pyridostigmine, and Edrophonium

The pharmacokinetics of edrophonium, neostigmine, and pyridostigmine is summarized in Table 13-13.[641][642][643][644] The data indicate several relevant clinical conclusions:

1. Pyridostigmine has a longer elimination half-life than the other anticholinesterases do, which probably accounts for its longer duration of action.[641][642]
2. By comparing elimination half-lives in patients with and without renal failure, renal excretion accounts for about 50% of the excretion of neostigmine and about 75% of that of pyridostigmine and edrophonium. Renal failure decreases the plasma clearance of neostigmine, pyridostigmine, and edrophonium as much as if not more than that of the long-acting neuromuscular blockers. Therefore, if proper doses of anticholinesterase drugs are given and overdoses of neuromuscular blockers are avoided, renal failure should not be associated with "recurarization."[641][642] This remote possibility is further diminished if the clinician restricts relaxant administration to intermediate- or short-acting drugs in patients with renal failure.
3. Edrophonium was once thought to be an unsuitable antagonist in clinical practice because its duration of action was believed to be too short. However, when larger doses (i.e., 0.5 to 1.0 mg/kg) are given, sustained antagonism of a nondepolarizing neuromuscular blockade results.[645][646] In fact, the elimination half-life of edrophonium is similar to that of neostigmine or pyridostigmine (see Table 13-13).[643]

Table 13-13 -- Pharmacokinetics of neostigmine (N), pyridostigmine (P), and edrophonium (E) in patients without and with renal failure

	Without Renal Failure			With Renal Failure		
	N	***P***	***E***	***N***	***P***	***E***
Distribution half-life ($t_{½}\alpha$, min)	3.4	6.7	7.2	2.5	3.9	7.0
Elimination half-life ($t_{½}\beta$, min)	77	113	110	181	379	304
Volume of central compartment (L/kg)	0.2	0.3	0.3	0.3	0.4	0.3
Total plasma clearance (mL/kg/min)	9.1	8.6	9.5	4.8	3.1	3.9

Data from Cronnelly and colleagues[641][642] and Morris and colleagues.[643][644]

Mild hypothermia (i.e., 34°C to 35°C), as commonly occurs intraoperatively, has an impact on the pharmacokinetics of neostigmine. Its clearance is decreased from 16.2 mL/kg/min at 36.5°C to 13.5 mL/kg/min at 34.5°C.[494] Furthermore, the onset of peak effect of neostigmine is prolonged by mild hypothermia from 4.2 to 5.5 minutes.[494] If hypothermia has any influence on the efficacy of neostigmine-induced reversal, it is more likely to be due to the effect of temperature on the neuromuscular blocker (e.g., prolonged duration of action[477]) than the pharmacology of neostigmine.

The pharmacokinetics of the anticholinesterases depends on several factors, including metabolism as well as distribution and elimination. In the case of neostigmine, a carbamylated complex with acetylcholinesterase is formed,[576][578][647] and it is the rate of dissociation of neostigmine from this complex (i.e., its metabolism) that is probably the major determinant of its duration of action. The decay in its plasma concentration (i.e., its distribution and elimination) may not be as pertinent a determinant of the duration of action of the drug.[648]

Other Antagonists of Nondepolarizing Neuromuscular Blockade

Work is ongoing with a completely novel type of antagonist. This compound, ORG 25969 (Fig. 13-32), is a γ-cyclodextrin.[649][650][651][652] It is highly water soluble with a hydrophobic cavity that can encapsulate steroidal neuromuscular blocking drugs.[649][650][651][652] ORG 25969 exerts its effect by forming tight complexes with steroidal neuromuscular blocking drugs (rocuronium > vecuronium ≫ pancuronium),[649][650][651][652] and in so doing, the neuromuscular blocker is no longer available to bind with the acetylcholine receptor. ORG 25969 acts as a chelating agent, and it has no effect on acetylcholinesterase. This property eliminates the need for anticholinergic drugs. The compound's efficacy as an antagonist does not appear to rely on renal excretion of the cyclodextrin-relaxant complex.[653] Although a change in acid-base status will affect anticholinesterase activity, it does not appear to influence the efficacy of ORG 25969.[654] In male volunteers, administration of 8 mg/kg ORG 25969 3 minutes after rocuronium (0.6 mg/kg) resulted in recovery of the TOF ratio to 0.9 within 2 minutes.[655]

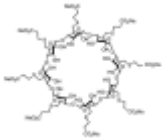

Figure 13-32 Structure of the synthetic γ-cyclodextrin (ORG 25969).

SPECIAL POPULATIONS

Pediatric Patients

The development of the neuromuscular junction is not complete at birth.[17][656] In humans, maturation of neuromuscular transmission probably occurs after the first 2 months of age.[657] Nonetheless, neuromuscular blockers can be used safely in term and preterm infants.

Routine administration of succinylcholine to healthy children should be discontinued. In apparently healthy children, intractable cardiac arrest with hyperkalemia, rhabdomyolysis, and acidosis may develop after succinylcholine administration, particularly in patients with unsuspected muscular dystrophy of the Duchenne type.[658][659] In response to this potential adverse effect, the U.S. Food and Drug Administration and Glaxo-Wellcome have modified the package insert for succinylcholine by adding a warning against the use of succinylcholine in children except for emergency control of the airway (see the section on complications of succinylcholine; also see Chapter 60).

It is not apparent from older studies whether newborns are more sensitive than adults to nondepolarizing neuromuscular blockers.[660][661][662][663] More recent studies by Fisher and colleagues[241][664][665] on the pharmacokinetics and pharmacodynamics of neuromuscular blockers in infants, children, and adults, however, have made it possible to better understand the clinical pharmacology of these drugs in pediatric patients (see Chapter 60). Neonates and infants are more sensitive than adults to the neuromuscular blocking effects of dTc.[664] A lower plasma concentration of this neuromuscular blocker is required to achieve a desired level of neuromuscular blockade in these young patients. However, the dosage should not be decreased because infants have a larger volume of distribution. The increased volume of distribution and slower clearance (Fig. 13-33) contribute to a longer elimination half-life,[664][666] which means that in infants, dTc may require less frequent dosing (longer dosing intervals) than in older children.

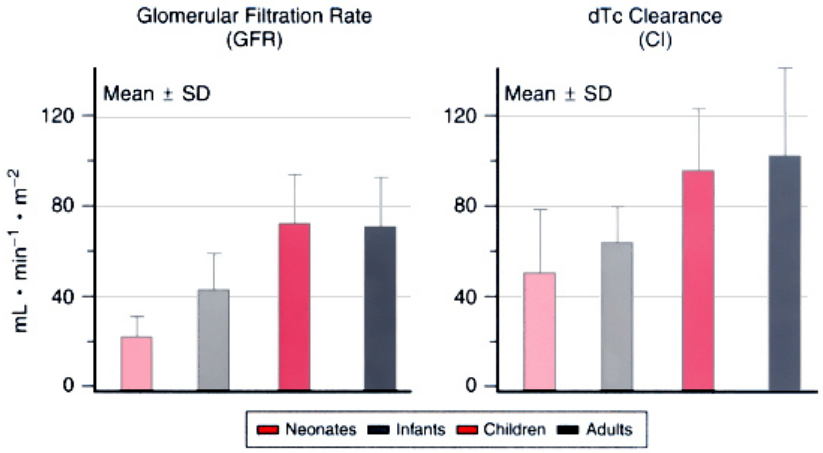

Figure 13-33 Correlation between age, glomerular filtration, and clearance of *d*-tubocurarine (dTc).
(Redrawn from Fisher DM, O'Keeffe C, Stanski DR, et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. Anesthesiology 57:203–208, 1982.)

Atracurium, vecuronium, cisatracurium, rocuronium, and mivacurium are commonly administered to children. The popularity of these drugs in children most likely stems from the following points: minimal residual paralysis is seen in the postoperative period,[667][668] and a faster onset of action occurs in children than in adults.

Atracurium and vecuronium, in comparison, show very different kinetic and dynamic patterns in infants. As with the long-acting neuromuscular blockers, the sensitivity of infants to vecuronium is greater than it is in children (ED_{95} of 0.047 versus 0.081 mg/kg, respectively).[669] The increased duration of action in infants is most likely secondary to the increased volume of distribution of vecuronium because its clearance is unchanged.[665][666] Vecuronium therefore acts as a long-acting neuromuscular blocker in neonates.[665][666][670]

In contrast, the duration of action of atracurium is not significantly different in pediatric patients than it is in adults.[671][672][673] As with vecuronium and dTc, the volume of distribution is increased in infants.[241] However, clearance of atracurium is also more rapid.[241] Therefore, the same dose (0.5 to 0.6 mg/kg) can be used in infants, children, and adults for tracheal intubation without any major difference in its duration of action in the three groups. In children, a dose of 0.1 mg/kg cisatracurium has an onset of just over 2 minutes and a clinical duration of approximately 30 minutes during balanced or halothane anesthesia.[674] The calculated ED_{95} doses of cisatracurium in infants and children are 43 and 47 mg/kg, respectively.[675] The mean infusion rate necessary to maintain 90% to 99% neuromuscular blockade is also similar in infants and children.[676]

Rocuronium in adults is an intermediate-acting neuromuscular blocker with a fast onset of action, and the same is also true in infants and children.[676][677] Its potency is greater in infants than children, but its onset is faster in the latter age group.[677] In children,

rocuronium, 0.6 mg/kg, produces better conditions for rapid tracheal intubation than vecuronium, 0.1 mg/kg, or atracurium, 0.5 mg/kg, does.[676] If given by intramuscular injection into the deltoid (1.0 mg/kg in infants and 1.8 mg/kg in children), rocuronium allows for tracheal intubation in approximately 3 minutes.[678][679] However, intramuscular injection is not recommended as an alternative to rapid-sequence induction.[679] As with adults, for rapid-sequence intubation (60 seconds) in the presence of a full stomach, a 1.2-mg/kg dose of rocuronium is suggested.

The ED_{95} of mivacurium is greater in children than adults (0.10 mg/kg during narcotic anesthesia and 0.09 mg/kg during halothane anesthesia).[680] Children therefore require larger doses of mivacurium than adults do to achieve a given depth of neuromuscular blockade.[680][681] Onset time, as with atracurium[670] and vecuronium,[682] is faster in children than adults, so maximal block is achieved in less than 2 minutes. A dose of 0.25 to 0.30 mg/kg facilitates tracheal intubation in about 90 seconds in children. A dose of twice the ED_{95} (0.2 mg/kg) results in only a 20% increase in the duration of blockade as compared with the ED_{95}.[681] In contrast to adults, large doses have less of a propensity to cause histamine release. Facial flushing and transient hypotension are observed in about 10% to 15% of the pediatric population who receive 0.25 mg/kg mivacurium as a rapid 5- to 10-second injection.[680] Mivacurium's clinical duration of action is shorter in children than adults (12 versus 15 to 20 minutes). Because of its short duration of action, mivacurium is best used as an infusion in children for maintenance of relaxation. Infusion rates required by children (10 to 20 µg/kg/min) are about twice those required by adults, probably because of significantly higher butyrylcholinesterase activity.[683][684]

Antagonism of residual neuromuscular blockade in the case of the various nondepolarizers is similar in children and adults. Fisher and associates[629][685] described some minor variations in the neostigmine and edrophonium dosage for pediatric patients. For example, the ED_{50} of neostigmine for antagonism of a dTc-induced 90% block of the adductor pollicis twitch was 22.9 µg/kg in adults versus 15.5 µg/kg in infants.[629] In the case of edrophonium, the ED_{50} for antagonism of a dTc-induced 90% block was 128 µg/kg in adults. In children, the ED_{50} was 233 µg/kg, and in infants the ED_{50} was 145 µg/kg.[685] The rate of recovery of intermediate- or short-acting neuromuscular blockers is faster than that of long-acting drugs in children.[583][686]

Neostigmine doses of up to 50 to 60 µg/kg or edrophonium doses of 500 to 1000 µg/kg should be used for antagonism of residual neuromuscular blockade in children. In all cases, tests of clinical recovery, such as head lift, leg lift, and cry, should be performed and documented for pediatric patients and adults.

Elderly Patients (also see Chapter 62)

The pharmacodynamics of neuromuscular blockers is altered in elderly patients. A number of physiologic changes accompany the aging process, including decreases in total-body water, increases in total-body fat, decreases in hepatic and renal blood flow, and decreases in cardiac reserve, which account for the altered responses of the elderly to neuromuscular blockers. A number of physiologic and anatomic changes at the neuromuscular junction also occur with aging. These changes include an increase in the distance between the

junctional axon and the motor end plate, flattening of the folds of the motor end plate, a decreased concentration of acetylcholine receptors at the motor end plate, a decrease in the amount of acetylcholine in each vesicle in the prejunctional axon, and decreased release of acetylcholine from the preterminal axon in response to a neural impulse.[687] As shown by Matteo and coworkers,[688] despite these age-related changes, acetylcholine receptor sensitivity to nondepolarizing neuromuscular blockers is not altered by advancing age (Fig. 13-34). That is, the elderly and young adults have similar degrees of neuromuscular blockade at the same plasma concentration of a neuromuscular blocker. Rather, it appears that in the elderly, decreased splanchnic and renal blood flow, decreased glomerular filtration rate, and decreased hepatic function are responsible for the prolonged duration of action of most neuromuscular blockers. The greater depth of blockade with a given dose of relaxant in elderly patients versus young patients may also be due in part to altered volumes of distribution. The impact of aging alone, versus disease states often associated with the aging process, may be difficult to distinguish when identifying mechanisms of altered neuromuscular blocker action in the elderly.

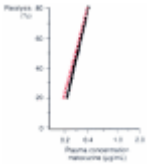

Figure 13-34 Correlation of plasma metocurine concentration versus percent paralysis (twitch depression) in young and elderly patients *(open and closed circles)*. Differences are not significant.
(Redrawn from Matteo RS, Backus WW, McDaniel DD, et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine and metocurine in the elderly. Anesth Analg 64:23–29, 1985.)

Pancuronium,[688][690] metocurine,[688] dTc,[688] vecuronium,[569][665][691] and rocuronium[354] all show altered pharmacodynamics and pharmacokinetics in the elderly patient population. Decreased clearance of each of these drugs from plasma explains the prolonged duration of action in these patients. These neuromuscular blockers depend on the kidney or the liver (or both) for their metabolism and elimination.

Surprisingly, the pharmacokinetics and pharmacodynamics of the long-acting neuromuscular blockers doxacurium[692] and pipecuronium,[693] which rely almost exclusively on the kidney for elimination, do not seem to be significantly different in the elderly. The duration of neuromuscular blockade induced by doxacurium has been found to be more variable in the elderly than in younger patients and tends to be longer. However, clearance and elimination half-lives are the same in the two patient groups. Similarly, recovery from pipecuronium-induced neuromuscular blockade, the volume of distribution, clearance, and the elimination half-life of the drug are the same in young and old patients. Further studies in the elderly with doxacurium and pipecuronium may be needed to better define this issue.

In the case of drugs whose elimination is independent of hepatic or renal blood flow, their pharmacokinetics and pharmacodynamics should be unaffected by age. This is true of atracurium, which depends on Hofmann degradation for its clearance.[242][694] Cisatracurium, which also undergoes Hofmann elimination, has a delayed onset of effect in elderly patients.[343][359] The duration of action of the relaxant, however, appears to not be

influenced by advanced age. The prolonged elimination half-life of the drug in the elderly is due to an increased volume of distribution. Clearance is not decreased with advanced age.

Butyrylcholinesterase activity in the elderly, though still in the normal range, is decreased by approximately 26% when compared with that in young adults.[695] Because mivacurium is metabolized by butyrylcholinesterase, its clearance is likely to be slightly reduced in the elderly; as a result, the duration of action is 20% to 25% longer,[696] and the infusion requirement to maintain a stable depth of blockade is decreased.[697]

In general, when maintaining a neuromuscular blockade with nondepolarizing neuromuscular blockers in elderly patients, one can expect that with the exception of atracurium and cisatracurium, the dosing interval will be increased and fewer doses of neuromuscular blocker will be required to maintain the desired depth of neuromuscular blockade. The choice of agent and the use of monitoring of the depth of blockade are exceptionally important in this population because recovery of neuromuscular function is generally delayed in the elderly. Inadequate or incomplete recovery of muscle strength after the use of pancuronium is associated with an increased incidence of perioperative pulmonary complications in this patient population.[60]

Obese Patients

Reports are conflicting concerning the effect of obesity on the pharmacodynamics of nondepolarizing neuromuscular blockade.[698][699][700] Although the duration of action of pancuronium is unaffected by patient weight,[700] obese patients recover more slowly from doxacurium-,[701] vecuronium-,[702] or rocuronium-induced[703] neuromuscular blockade. These findings imply that elimination of these drugs is decreased. Recovery from atracurium-induced neuromuscular blockade is not affected by obesity,[702] which is most likely secondary to its lack of dependence on end-organ function for elimination.

Neuromuscular blockers should be dosed in obese patients on the basis of about 20% more than lean body mass rather than on actual body weight[704] to ensure that these patients are not receiving relative overdoses.

Severe Renal Disease (also see Chapter 56)

Renal failure influences the pharmacology of nondepolarizing neuromuscular blockers by producing either decreased elimination of the drug or its metabolites via the kidney or decreased activity of butyrylcholinesterase (Table 13-14). Consequently, the duration of action of neuromuscular blockers may be prolonged in patients with renal failure. An early example of prolonged neuromuscular blockade as a result of renal failure was a case of postoperative respiratory failure after gallamine, reported in 1950.[710]

Renal failure does not alter the sensitivity (dose-response relationship) of patients to the neuromuscular blocking action of gallamine,[347] dTc,[711] pancuronium,[234] atracurium,[712] vecuronium,[713] rocuronium,[714] or mivacurium,[715] but it does cause resistance to metocurine.[345]

Gallamine[347] and metocurine,[345] which rely almost exclusively on the kidney for their elimination, have reduced plasma clearance and potentially a very long duration of action in patients with renal failure (see Table 13-14). Pancuronium and dTc are eliminated predominantly by the kidney, and renal failure is associated with reduced plasma clearance and an increased elimination half-life for these drugs as well.[190][716] As a consequence of these pharmacokinetic changes, the duration of neuromuscular blockade produced by these drugs is longer and more variable than in patients with normal renal function.[716] In patients with renal failure, doxacurium has decreased plasma clearance, an increased elimination half-life, and a prolonged duration of action.[346][717] Pipecuronium is eliminated predominantly by the kidney.[293] Its plasma clearance is decreased by one third, and its elimination half-life is increased twofold in patients with renal failure.[298] Because of the potential for prolonged block and the availability of intermediate- and short-acting neuromuscular blockers, there is no longer any reason to recommend the use of long-acting neuromuscular blockers in patients with renal failure.

The pharmacokinetics and duration of action of atracurium are unaffected by renal failure.[705][718][719] This lack of effect is due in part to the fact that Hofmann elimination and ester hydrolysis[340] account for 50% of its total clearance.[326] The elimination half-life of laudanosine, the principal metabolite of atracurium, increases in renal failure.[705][720] Recent evidence suggests, however, that significant concentrations of laudanosine are not achieved during the administration of atracurium in the operating room setting.[705][720]

In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged.[257] Hofmann elimination accounts for 77% of the total clearance of cisatracurium,[342] and renal excretion accounts for 16% of its elimination.[342] Clearance of the drug is slightly decreased by 13% in this patient population.[721]

Vecuronium relies principally on hepatic, not renal mechanisms for its elimination.[303][707] However, its clearance is reduced and its elimination half-life is increased in patients with renal failure.[706][708][709] In one study, the duration of action of vecuronium, 0.1 mg/kg, was both longer and more variable in patients with renal failure than in those with normal renal function.[709] In three other studies, the duration of action of 0.05 to 0.14 mg/kg vecuronium was not prolonged by renal failure, but this result was probably due to the use of relatively small doses or inadequate sample sizes.[303][706][708] The principal metabolite of vecuronium, 3-desacetylvecuronium, has 80% of the neuromuscular blocking activity of vecuronium[302]; it may cause prolonged paralysis in patients with renal failure in the ICU.[305][722] In patients with renal failure, the duration of action and rate of recovery from vecuronium- or atracurium-induced neuromuscular blockade during surgery are similar.[549][723][724]

The plasma clearance of rocuronium may be decreased in patients with renal failure[725] and its distribution volume increased.[352] The duration of action of single and repeated doses, though, is not significantly affected.[714] When rocuronium is administered to patients with renal failure who are undergoing renal transplantation versus patients with normal renal function, plasma clearance is unchanged (2.89 mL/kg/min), the volume of distribution is increased by 28%, and the elimination half-life is lengthened by 37% (see Fig. 13-17).[352][726]

The effect of renal failure on the duration of action and recovery from mivacurium-induced blockade is variable. In some studies, renal failure had no effect,[228] whereas in others, the duration of action and recovery were prolonged and the infusion dose requirements were decreased by renal failure.[727] The effect of renal failure on mivacurium's duration of action is most probably mediated through its effect on butyrylcholinesterase. Renal failure can decrease butyrylcholinesterase activity,[728] and this decrease would be expected to prolong the duration of mivacurium-induced neuromuscular blockade.[320][729] Clearance of the *cis-trans* and *trans-trans* isomers of mivacurium is decreased by approximately 20% in those with renal failure.[314] In the studies in which renal failure had no effect on mivacurium's duration of action, butyrylcholinesterase activity was similar in patients with and without renal failure.[228] In contrast, when patients with renal failure had decreased butyrylcholinesterase activity, the duration of action of mivacurium was longer.[318][727] Because a patient's butyrylcholinesterase activity is not known preoperatively, when mivacurium is used in patients with renal failure, doses should be conservative, and its effect should be carefully monitored.

Hepatobiliary Disease (also see Chapter 56)

Patients with hepatobiliary disease may exhibit prolonged blockade with dTc,[730] pancuronium,[296] doxacurium,[346] vecuronium,[231] rocuronium,[353][357] and mivacurium.[172][228] In the case of pancuronium,[295] vecuronium,[231] and mivacurium,[172][228] this prolonged action is associated with decreased plasma clearance of the drug. However, this relationship is not consistent, and many studies have described a reduction in clearance without a prolonged duration of action. In the case of atracurium, one study even reports increased clearance in patients with cirrhosis, but the duration of action was normal.[330]

The influence of hepatobiliary disease on the pharmacokinetics of neuromuscular blockers is complex (Table 13-15). In most studies, hepatic disease is associated with an increased volume of distribution, and as a result, patients have an apparent resistance to the effect of dTc,[330][735] pancuronium,[297][736] atracurium,[737] and rocuronium.[732] The effect of hepatic disease on the pharmacokinetics of neuromuscular blockers (see Table 13-15) suggests that initial doses may need to be greater than for patients with normal hepatic function but that once the desired level of block has been achieved, subsequent recovery may be slower. This is illustrated in the case of vecuronium, in which doses up to 0.15 mg/kg have a normal duration of action[304][738][739] but a dose of 0.2 mg/kg has prolonged action (see Fig. 13-15).[731][739]

Hepatic disease can alter the elimination of neuromuscular blockers by several mechanisms. The principal route of metabolism of pancuronium and vecuronium is deacetylation at the 3-position.[290][292] This metabolic process is presumed to occur in the liver because 10% to 20% of the total dose of pancuronium and 40% percent of the total dose of vecuronium are found in the liver and bile as both parent drug and metabolite.[290][292][303] In hepatic disease, an increased plasma concentration of bile salts can reduce the hepatic uptake of pancuronium and vecuronium,[290][733] which may be an explanation for the decreased clearance of these drugs observed by some investigators.[294][296][346] Excretion of vecuronium is diminished in the presence of decreased hepatic function.[665] The duration of

action of vecuronium is longer in these patients, and recovery is slower than in young healthy individuals.

Atracurium and cisatracurium share organ-independent modes of elimination.[322][323][340][341][342] As a consequence, their clearance should be little affected by hepatic disease. In fact and in contrast to all other neuromuscular blockers, plasma clearance of atracurium and cisatracurium is slightly increased in patients with liver disease (see Table 13-15).[330][358] Because elimination of atracurium and cisatracurium occurs outside as well as from within the central compartment, it has been suggested that a larger distribution volume should be associated with a larger clearance.[342] In two studies,[330][358] volumes of distribution and clearance of the drugs increased with liver disease, thus lending support to this theory.[342] The increased clearance of the relaxant in patients with liver disease is not reflected in a decrease in the drugs' duration of action.[330][358]

A concern raised about administering atracurium to patients with hepatic disease was the possible accumulation of laudanosine.[339] Although laudanosine relies principally on hepatic mechanisms for elimination, the concentrations encountered during liver transplantation are unlikely to be associated with clinical sequelae.[339][735]

In patients with hepatic disease (most commonly cirrhosis), the distribution volume of rocuronium is increased,[353][356][357][732] and its clearance may be decreased.[357] The duration of action of rocuronium is prolonged in patients with hepatic disease,[353][357][732] and its onset may be prolonged.[353]

In patients with severe liver disease, butyryl-cholinesterase activity is decreased because of decreased synthesis of the enzyme in the liver.[228] Consequently, plasma clearance of the isomers of mivacurium is decreased by approximately 50% (see Table 13-15),[172] and its duration of action is prolonged and may be almost tripled.[172][228]

Burns

After a period of immobilization, burn injury causes upregulation of both fetal ($\alpha_2\beta\gamma\delta$) and mature ($\alpha_2\beta$ϵ$\delta$) nAChRs.[740][741][742][743][744][745] Upregulation of nAChRs is usually associated with resistance to nondepolarizing neuromuscular blockers and increased sensitivity to succinylcholine.[746] Causes of upregulation of nAChRs are listed in Table 13-16. A significant increase in the quantal content of evoked acetylcholine release is noted by 72 hours after scald injury in rats.[747] This increased acetylcholine release also contributes to the resistance to nondepolarizing blockers in burn patients. In mice, thermal injury induces changes in diaphragm acetylcholinesterase with respect to total content and specific molecular forms.[748]

Table 13-16 -- Conditions associated with upregulation and downregulation of acetylcholine receptors

nAChR Upregulation	nAChR Downregulation
Spinal cord injury	Myasthenia gravis

nAChR Upregulation	nAChR Downregulation
Stroke	Anticholinesterase poisoning
Burns	Organophosphate poisoning
Prolonged immobility	
Prolonged exposure to neuromuscular blockers	
Multiple sclerosis	
Guillain-Barré syndrome	
nAChR, nicotinic acetylcholine receptor.	

From Naguib M, Flood P, McArdle JJ, et al: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. Anesthesiology 96:202–231, 2002.

Anesthetic Implications

Resistance to the effects of nondepolarizing neuromuscular blocking drugs is usually seen in patients with greater than 25% total-body surface area burns.[244][746] Recovery of neuromuscular function to preburn levels may take several months[749] or even years after the burn injury.[750] The increase in serum potassium that normally follows succinylcholine administration is markedly exaggerated in burned victims.[119][751] Potassium concentrations as high as 13 mEq/L and resulting in ventricular tachycardia, fibrillation, and cardiac arrest have been reported.[751][752] The magnitude of the hyperkalemic response does not appear to closely correlate with the magnitude of the burn injury. Potentially lethal hyperkalemia was seen in a patient with only an 8% total-body surface area burn.[753] Succinylcholine has been safely administered within 24 hours of a burn injury. After this initial 24 hours, however, sufficient alteration in muscle response may have occurred, and the use of succinylcholine is best avoided.

The time course of abnormal muscle membrane function corresponds with that of the healing process. Once normal skin has regrown and any infection has subsided, return of normal acetylcholine receptor populations appears to occur.[754] Normal responses to succinylcholine have been demonstrated in burn patients studied 3 years postinjury.[754] The length of time during which a burn patient may be at risk for a hyperkalemic response is not well defined. A conservative guideline would therefore be to avoid the use of succinylcholine in patients 24 to 48 hours after a thermal injury and for at least 1 to 2 years after the burned skin has healed.

Neuromuscular Blockers and Weakness Syndromes in the Critically Ill (also see Chapter 74 and Chapter 75)

Neuromuscular blocking drugs are frequently used in conjunction with sedatives and analgesics in the ICU. Indications for the use of neuromuscular blockers in the ICU are outlined in Table 13-17. Few data support their use, and evidence for a beneficial effect on pulmonary function or patient oxygenation is inconclusive.[755][756][757][758] Nonetheless, nondepolarizing neuromuscular blockers are commonly used for weeks in ICU patients,

most of the time without monitoring and frequently at doses exceeding those used in the operating room.[759][760] The results of two surveys in the United States, including anesthesiologists and nurses with special certificates of competence in critical care, indicate that 98% of those surveyed use neuromuscular blocking drugs at least occasionally.[759][760]

Table 13-17 -- Reported indications for use of muscle relaxants in the intensive care unit

Facilitate mechanical ventilation
Facilitation of endotracheal intubation
Enable patient to tolerate mechanical ventilation
High pulmonary inflation pressures, e.g., acute respiratory distress syndrome
Hyperventilation for increased intracranial pressure
Facilitate therapeutic or diagnostic procedures
Tetanus
Status epilepticus
Reduce oxygen consumption
Abolish shivering
Reduce work of breathing

Of particular concern in intensive care settings is the risk of paralyzed patients receiving inadequate analgesia and sedation.[761][762][763] This may be due to the fact that ICU nurses and physicians are unfamiliar with the pharmacology of the neuromuscular blocking drugs.[759][762] For instance, pancuronium was thought to be an anxiolytic by 50% to 70% of ICU nurses and house staff, and 5% to 10% thought that it was an analgesic.[762] In the United Kingdom, the erroneous use of neuromuscular blockers as sedatives in intensive care was not uncommon in the 1980s.[764][765][766] Approximately 96% of ICU patients received neuromuscular blockers to aid mechanical ventilation in 1980. By 1986, their use had fallen to 16% of ventilated patients.[764][765][766] This marked reduction followed the publication of patients' ordeals who were paralyzed while conscious in the ICU.[15] In the United States, neuromuscular blockers are used in less than 20% of all patients requiring mechanical ventilation.[759]

Prolonged ICU stay during critical illness is associated with disorders of neuromuscular function that contribute to morbidity, increased length of hospital stay, weaning difficulties, and prolonged rehabilitation.[767][768] Complications of long-term administration of neuromuscular blockers in the ICU are outlined in Table 13-18. In the ICU, the duration of mechanical ventilation, sepsis, dysfunction of two or more organs, female gender, administration of steroids, and hypercapnia are known risk factors for neuromuscular dysfunction.[769][770][771] Syndromes of weakness in critically ill patients are relatively common and probably polymorphic in origin. In a retrospective study of 92 critically ill patients with clinically diagnosed weakness, electromyographic studies indicated that acute

myopathy (critical illness myopathy) is three times as common as acute axonal neuropathy (critical illness neuropathy) (43% versus 13%, respectively).[767] The additional health care cost of one case of persistent weakness was estimated to be approximately $67,000.[772] The differential diagnosis of neuromuscular weakness in the ICU is listed in Table 13-19.

Table 13-18 -- Complications of muscle paralysis in the intensive care unit

Short-term use
Specific, known drug side effects
Inadequate ventilation in the event of ventilator failure or circuit disconnection
Inadequate analgesia and/or sedation
Long-term use
Complications of immobility
Deep venous thrombosis and pulmonary embolism
Peripheral nerve injuries
Decubitus ulcers
Inability to cough
Retention of secretions and atelectasis
Pulmonary infection
Dysregulation of nicotinic acetylcholine receptors
Prolonged paralysis after stopping relaxant
Persistent neuromuscular blockade
Critical illness myopathy
Critical illness polyneuropathy
Combination of the above
Unrecognized effects of drug or metabolites
Succinylc holine and metabolic acidosis/hypovolemia
3-Desacetylvecuronium and neuromuscular blockade
Laudanosine and cerebral excitation

Table 13-19 -- Causes of generalized neuromuscular weakness in the intensive care unit

Central nervous system
Septic or toxic-metabolic encephalopathy
Brainstem stroke

Central pontine myelinolysis
Anterior horn cell disorders (e.g., amyotrophic lateral sclerosis)
Peripheral neuropathies
Critical illness polyneuropathy
Guillain-Barré syndrome
Porphyria
Paraneoplastic
Vasculitis
Nutritional and toxic
Neuromuscular junction disorders
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Botulism
Prolonged neuromuscular junction blockade
Myopathies
Critical illness myopathy
Cachectic myopathy
Rhabdomyolysis
Inflammatory and infectious myopathies
Muscular dystrophies
Toxic
Acid maltase deficiency
Mitochondrial
Hypokalemia
Hypermetabolic syndromes with rhabdomyolysis (e.g., neuroleptic malignant syndrome)

From Lacomis D: Critical illness myopathy. Curr Rheumatol Rep 4:403–408, 2002.

Critical Illness Myopathy

Lacomis and colleagues[773] suggested using the term "critical illness myopathy" (CIM) instead of the current terminology used in the literature such as acute quadriplegic myopathy,[774] acute (necrotizing) myopathy of intensive care,[775] thick filament myopathy, acute corticosteroid myopathy,[776] and critical care myopathy.

Most published reports of CIM in the ICU have focused on patients with status asthmaticus.[777][778][779] Affected individuals have typically been treated with corticosteroids and nondepolarizing neuromuscular blockers. Nevertheless, myopathy has also been documented in asthmatic patients, in those with chronic lung disease without paralysis who received corticosteroids,[780][781] and in critically ill patients with sepsis who received neither corticosteroids nor nondepolarizing neuromuscular blockers.[782][783] Animal studies found that the number of cytosolic corticosteroid receptors is increased in immobilized muscles relative to contralateral controls.[784] It seems—at least in some patients—that prolonged immobility may be the key risk factor for myopathy in corticosteroid-treated patients[785] and that selective muscle atrophy is a result of changes in glucocorticoid sensitivity.[784]

Sepsis, immobility, and the catabolism associated with negative nitrogen balance may also result in myopathy.[17][768] Skeletal muscle hypoperfusion is noted in patients with severe sepsis despite normal or elevated whole blood oxygen delivery.[786] Antibodies to nAChRs have been demonstrated in a rodent model of sepsis.[787] This myasthenialike syndrome is also seen in critically ill patients. Evidence of local immune activation by cytokine expression in skeletal muscles was reported in patients with CIM.[788]

The major feature of CIM is flaccid weakness that tends to be diffuse and often includes the facial muscles and the diaphragm.[773] The clinical features of CIM overlap with those of critical illness polyneuropathy (CIP) and prolonged neuromuscular blockade.[773] Electrophysiologic studies and increases in serum creatine kinase concentrations may differentiate neuropathy from myopathy.[773] Lacomis and coauthors[773] stated that "muscle biopsy should be considered if another myopathic process such as an inflammatory myopathy is suspected or if the histologic findings would affect management."

Critical Illness Polyneuropathy

The polyneuropathy seen in the critically ill has been termed critical illness polyneuropathy. CIP affects both sensory and motor nerves and occurs in 50% to 70% of patients with multisystem organ failure and systemic inflammatory response syndrome (SIRS).[789][790][791][792] It has been postulated that SIRS contributes to CIP by releasing cytokines and free radicals that damage the microcirculation of the central and peripheral nervous systems.[788][781] Dysregulation of the microcirculation may render the peripheral nervous system susceptible to injury.[793]

No specific treatment is available for weakness syndromes in critically ill patients other than physical rehabilitation. Intravenous immunoglobulin and nerve growth factors appear to be promising in CIP syndrome.[794][795] Recently, intensive insulin therapy during critical illness has been found to decrease the risk of CIP.[796][797] Maintenance of blood glucose at or below 110 mg/mL in critically ill patients may reduce the risk of CIP.[796][797]

The outcomes from CIM and CIP appear to be similar.[767] The reported mortality rate of patients with CIP syndrome is about 35%.[798] In one study, 100% of the patients (13 of 13) who survived had abnormal clinical or neurophysiologic findings 1 to 2 years after the onset of CIP syndrome.[799] The quality of life was markedly impaired in all patients.[799]

Clinical Implications

Should Succinylcholine Be Used in ICU Patients?

It is likely that upregulation of nAChRs induced by immobilization and by prolonged administration of nondepolarizing neuromuscular blockers[800][801][802] contributes to (1) the higher incidence of cardiac arrest associated with the use of succinylcholine in ICU patients[803][804] and (2) the increased requirements for nondepolarizing neuromuscular blockers in ICU patients.[802][805][806][807] Upregulation of nAChRs was noted in the muscles of deceased critically ill adults who had received long-term infusions of vecuronium.[803] Therefore, succinylcholine is best avoided in ICU patients when total-body immobilization exceeds 24 hours.[17] In a recent survey in U.K. ICUs, 68.7% of the respondents indicated that they would use succinylcholine in a clinical scenario suggestive of CIP.[808] This result highlights the lack of awareness of the dangers associated with the use of succinylcholine in these patients.[808]

Should Nondepolarizing Neuromuscular Blockers Be Used in ICU Patients?

Nondepolarizing neuromuscular blocker-associated persistent weakness appears to be a distinct pathologic entity and is not simply a manifestation of weakness syndromes in the critically ill.[789] A prospective study by Kupfer and associates[809] showed a 70% incidence of persistent weakness in ICU patients who received neuromuscular blockers for more than 2 days versus a 0% incidence in similar ICU patients who received no neuromuscular blocker. This study is compelling evidence for the role of nondepolarizing neuromuscular blockers in this complication.

Long-term weakness has been described after all commonly used nondepolarizing neuromuscular blockers.[305][777][779][810][811] The overall incidence of prolonged paralysis after long-term use of neuromuscular blockers is about 5%. Approximately 20% of patients who received neuromuscular blockers for more than 6 days,[810] 15% to 40% of asthmatic patients who also received high-dose steroids,[776][778] and 50% of patients with renal failure who received vecuronium suffered prolonged weakness.[305] Clinically, it appears that prolonged recovery from neuromuscular blockade occurs more frequently when steroidal neuromuscular blockers are used.[305][810]

However, prolonged weakness was also noted after the use of atracurium in ICU patients.[811] Furthermore, the use of atracurium has raised concern regarding its metabolite laudanosine. Laudanosine is also detected in the cerebrospinal fluid (CSF) of ICU patients who receive atracurium.[812] It is an analeptic and can trigger seizures in animals.[813] The toxic dose in humans is not known, but case reports have described patients having seizures while receiving atracurium, and laudanosine has not been ruled out as a cause of these seizures.[814][815][816] Some evidence has also shown that laudanosine can activate neuronal nicotinic receptors.[817] Cisatracurium is a single isomer of atracurium, and because it is four to five times more potent than atracurium, it is given in smaller doses. Therefore, the risk of laudanosine-related adverse effects should be minimal.[336][818][819]

Nondepolarizing neuromuscular blockers are polar molecules and do not readily cross the blood-brain barrier, but vecuronium and its long-acting active metabolite (3-desacetylvecuronium) have been detected in the CSF of patients in the ICU. The CNS

effects of neuromuscular blockers and their metabolites in humans have not been well studied, but in rats, atracurium, pancuronium, and vecuronium injected into the CSF will cause dose-related cerebral excitation culminating in seizures.[813] Cerebral excitation with consequent increased cerebral oxygen demand is undesirable in ICU patients at risk for cerebral ischemia. It has also been suggested that nondepolarizing neuromuscular blockers can gain access to nerves during SIRS and directly result in neurotoxicity.[793][813][820]

Combining corticosteroids and nondepolarizing neuromuscular blockers should be avoided.[821] When nondepolarizing neuromuscular blockers are necessary, the use of a peripheral nerve stimulator is recommended, and periodic return of muscle function should be allowed. However, routine monitoring of neuromuscular function alone is not sufficient to eliminate prolonged recovery and weakness syndromes in ICU patients.[822] Adjusting the dosage of neuromuscular blockers by peripheral nerve stimulation versus standard clinical dosing in critically ill patients reduces drug requirements, produces faster recovery of neuromuscular function, and results in a total cost savings of $738 per patient.[823] A recent study found that daily interruption of sedative drug infusions decreases the duration of mechanical ventilation and length of stay in the ICU.[824] The impact of such an approach on the weakness syndromes in ICU patients is unknown. When nondepolarizing neuromuscular blockers are used, the guidelines in Table 13-20 may help minimize the incidence of complications. As stated in the clinical practice guidelines for sustained neuromuscular blockade in adult critically ill patients,[758]"*Independent of the reasons for using neuromuscular blockers, we emphasize that all other modalities to improve the clinical situation must be tried, using neuromuscular blockers only as a last resort*."

Table 13-20 -- Recommendations for the use of neuromuscular blockers in the intensive care unit

Avoid the use of neuromuscular blockers by
Maximal use of analgesics and sedatives
Manipulation of ventilatory parameters and modes
Minimize the dose of neuromuscular blockers
Use a peripheral nerve stimulator with train-of-four monitoring
Do not administer for more than 2 days continuously
Administer by bolus rather than infusion
Administer only when required and to achieve a well-defined goal
Continually allow recovery from paralysis
Consider alternative therapies
Avoid vecuronium in female patients with renal failure
Use isoflurane in place of muscle relaxants in severe asthmatics
Minimize the dose of steroid in asthmatics

Multiple sclerosis (MS), the most common demyelinating disease of the CNS, affects about 1 million people worldwide. The cause of MS is not known. Infectious agents, genetic predisposition, autoimmune reactions to antigens, and channel disease have been implicated in the etiology of MS.[825][826][827][828][829][830] Recently, it has been hypothesized that MS is a sexually transmitted disease.[828] Paralysis, sensory disturbances, autonomic disturbances, lack of coordination, and visual impairment are common features.[831] Axon loss correlates with permanent functional deficit.[832] It has been demonstrated that the CSF of patients with MS may contain a sodium channel-blocking factor (a local anesthetic-like factor).[833][834][835][836] This factor could explain the paresis seen in this disorder.[836] Therefore, it appears that channelopathies play an important role in the pathogenesis of this disorder.[827] In MS, the characteristics of individual skeletal muscles are similar to those observed in disuse myopathy.[837]

ANESTHETIC CONSIDERATIONS.

Autonomic dysfunction is seen in a significant number of patients with MS.[838][839] During anesthesia, careful attention should be paid to maintenance of adequate preload, temperature control, postural changes, blood loss, and peak airway pressure during mechanical ventilation. Patients with autonomic dysfunction demonstrate an exaggerated response to α-sympathomimetics.[840]

No conclusive evidence has shown that the stress of surgery and anesthesia may increase the rate of relapse in patients with MS.[841][842] The use of regional anesthesia in MS is more controversial. Both lumbar epidural anesthesia and subarachnoid anesthesia have safely been used in patients with MS.[843] However, some evidence suggests that hyperthermia[842] or higher concentrations of local anesthetic[841] may increase the relapse rate. In one study in which patients received either 0.5% or 0.25% bupivacaine for epidural anesthesia, relapses occurred only in patients receiving the higher dose of local anesthetic.[841]

As with any patient with denervation or disuse, or both, there may be upregulation in nAChR numbers and increased sensitivity to depolarizing neuromuscular blockers.[17] In this case, the patient is at risk for hyperkalemia after the administration of succinylcholine. Paradoxical reports have described increased sensitivity to nondepolarizing neuromuscular blockers in patients with MS, probably because of reduced muscle mass or reduced margin of safety for neuromuscular transmission.[844] Denervation is known to induce a reduction in the resting potential, and this decreased resting potential will significantly contribute to muscle weakness.[17][845][846] In these patients, small doses of short-acting neuromuscular blockers should be used along with adequate monitoring of neuromuscular function.

Motor Neuron Diseases

The motor neuron diseases are a group of diverse disorders characterized by muscle weakness, atrophy, spastic paralysis, or a combination of these findings as a result of involvement of lower or upper motor neurons.[17] Amyotrophic lateral sclerosis (ALS),

commonly known as Lou Gehrig's disease, is the most common motor neuron disease and has an incidence of 2 to 4 in 100,000. ALS is a progressive disease characterized by degeneration of cortical, brainstem, and spinal motor neurons.[847] The cognitive and sensory systems are usually spared. Kennedy's disease (spinobulbar muscular atrophy) affects lower motor neurons only. In contrast, hereditary spastic paraplegia involves upper motor neurons.[17]

Several mechanisms have been proposed to account for the progressive motor neuron death evident in ALS, including oxidative stress,[848] neurofilament damage,[849] mitochondrial abnormalities,[850] glutamate-mediated excitotoxicity,[851] and altered responses to hypoxia.[852] A role of oxidative stress has been suggested because mutations in the gene for Cu^{2+}/Zn^{2+} superoxide dismutase *(SOD1),* which catalyzes conversion of the $O_2^{\bullet}$ radical to O_2 and H_2O_2, have been identified in some 3% of all ALS cases.[848] In addition, antibodies to voltage-gated Ca^{2+} channels have been identified in ALS patients.[853] Treatment of ALS is aimed at symptomatic support.[847] Stem cell therapy may offer hope in the future.[854]

ANESTHETIC CONSIDERATIONS.

Patients with motor neuron disease are at risk for hyperkalemia after the administration of succinylcholine because of upregulation of nAChRs.[855] ALS patients have, in addition, presynaptic impairment of neuromuscular transmission,[856] which explains their hypersensitivity to nondepolarizing neuromuscular blockers.[857]

Respiratory muscle weakness frequently develops in patients with ALS, and most die of pulmonary complications.[858][859] Particularly in late stages of the disease, patients may be cachectic from inadequate nutrition and demonstrate reduced plasma protein binding for many of the anesthetic drugs.[17] These patients have reduced respiratory muscle reserve and abnormal airway protective reflexes and are at increased risk for respiratory depression and aspiration secondary to the use of sedative and anesthetic drugs.[17] Epidural anesthesia has been used in ALS patients without reported untoward effects.[860][861]

ALS is not believed to be associated with significant autonomic dysfunction. There is, however, evidence of sympathetic hyperactivity[862] and autonomic failure[863] accompanied by reduced baroreflex sensitivity.[864]

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is now considered to be a collection of diverse disorders with several clinical manifestations[865][866] and not simply as it was first described—"syndrome of symmetric, rapidly evolving flaccid paralysis and areflexia."[866] In addition to the demyelination seen in GBS, channelopathies have been identified.[827] GBS is not uncommon and has an incidence of 4 in 10,000.[865] Deaths are usually related to respiratory or autonomic dysfunction.

A sodium channel-blocking factor (a local anesthetic-like factor) has been identified in the CSF of patients with GBS.[833][834][836] This factor could contribute to the paralysis seen in this disorder.[836] There is also strong evidence for an association between certain infections and GBS.[865][867] Bacterial antigens are capable of initiating an immune response that

targets similar moieties on nerve fibers[866] or blocks both presynaptic voltage-gated calcium channels[868] and postsynaptic nAChR channels,[869] thereby leading to neuromuscular weakness. GBS patients commonly have symptomatic improvement after plasmapheresis.[870]

ANESTHETIC CONSIDERATIONS.

Demyelination or axonal degeneration produces functional denervation of the muscle and upregulation of nAChRs at the postsynaptic membrane. Succinylcholine is contraindicated because of the risk of hyperkalemic cardiac arrest.[871][872] This risk may persist after recovering from the symptomatic neurologic deficit.[873] Increased sensitivity to nondepolarizing neuromuscular blockers is expected in these patients because of the loss of motor units and channels blockade at the neuromuscular junction.[869][872][874]

Autonomic dysfunction is seen in approximately 60% of patients.[875] Asystole was reported after eyeball pressure, carotid sinus massage, and tracheal suction in patients with GBS.[876] During anesthesia, careful attention should be paid to maintenance of adequate preload, temperature control, postural changes, blood loss, and peak airway pressure during mechanical ventilation. Patients with autonomic dysfunction demonstrate an exaggerated response to α-sympathomimetics.[840]

Regional anesthesia is not contraindicated, although patients with GBS are sensitive to local anesthetics,[872][877] probably secondary to the presence of the sodium channel-blocking factor.[833][834][836] Because of the high incidence of autonomic instability, the slower onset of an epidural block may be preferable to the rapid onset of subarachnoid anesthesia.[17] GBS has been reported in four patients 1 to 2 weeks after epidural anesthesia. It was suggested that local trauma to nerve roots may initiate a cascade of immunologic events that result in demyelinating neuropathy in these patients.[878]

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease (CMTD; hereditary motor and sensory demyelinating polyneuropathy) is the most frequently occurring inherited peripheral neuropathy, with an incidence of 1 in 2500.[879] It has diverse genetic (autosomal dominant, X-linked, or autosomal recessive) and clinical manifestations.[880][881] Three genes responsible for CMTD type 1 have been identified: peripheral myelin protein 22 and myelin protein zero for the autosomal dominant form and connexin 32 for the X-linked dominant variant.[882] The latter variant encodes a gap junction protein.[881] Gap junctions are aggregations of channels made of proteins called connexins that are present in the plasma membrane.[883] In the nervous system, gap junctional channels play an essential role in the propagation of action potentials and in allowing rapid exchange of ions and nutrients.[884] Failure of gap junctions leads to impaired Schwann cell function and demyelination.

Peroneal nerve atrophy leading to weakness in the anterior and lateral compartments is the most common clinical manifestation in CMTD, but considerable variability exists in the pattern of atrophy. The sensory disturbance is milder than the motor disturbance.[17] Autonomic disturbances are occasionally reported.[885] Pregnancy may be associated with

exacerbations of CMTD, probably because of hormonal changes.[886][887] Respiratory insufficiency has also been described in patients with CMTD.[888]

ANESTHETIC CONSIDERATIONS.

CMTD patients have no evidence of a prolonged response to nondepolarizing neuromuscular blockers.[889][890] Although drugs that trigger malignant hyperthermia have been used in CMTD patients without untoward effects,[891][892] episodes of malignant hyperthermia have been reported in these patients.[893][894] Therefore, it is advisable to avoid using drugs known to trigger malignant hyperthermia.[17]

Patients with CMTD have been reported to be sensitive to the effects of thiopental.[885] However, propofol infusion has been safely used in these patients.[889][895] Respiratory insufficiency, vocal cord paresis, and cardiac conduction abnormalities have also been described in patients with CMTD.[888][896][897][898][899][900] Epidural anesthesia has been used successfully for labor and delivery in patients with CMTD.[901][902]

Primary Muscle Diseases

Muscular Dystrophies

Muscular dystrophies are a diverse group of genetically determined disorders of skeletal muscle and in some cases cardiac muscle.[903] They are characterized by muscle fiber necrosis and progressive muscle weakness.[903] The current classification of these disorders relies on molecular, genetic, and protein biochemical characterization (Table 13-21).[903]

Table 13-21 -- Molecular etiology of the muscular dystrophies

Diseases	Mode of Inheritance	Molecular Etiology	Reference
Duchenne	X-linked recessive	Absence of dystrophin	[904][924]
Becker	X-linked recessive	Reduced dystrophin	[905][924]
Emery-Dreifuss	X-linked recessive	Emerin	[906]
	Autosomal dominant	Lamin A/C	[907]
Limb-girdle	Autosomal dominant or recessive	Sarcoglycan deficiency	[908]
Congenital muscular dystrophy (CMD)	Autosomal recessive		
Classic CMD		Laminin α_2 chain	[909]
Fukuyama CMD		Fukutin	[910]
α_7 Integrin congenital myopathy		α_7 Integrin (laminin receptor)	[911]
Facioscapulohumeral	Autosomal dominant	4q35 rearrangements	[912]
Myotonic dystrophy (MD)	Autosomal dominant		

Diseases	Mode of Inheritance	Molecular Etiology	Reference
MD1		19q13 rearrangements	[913]
MD2		3q21 rearrangements	[914]

Modified from Naguib M, Flood P, McArdle JJ, et al: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. Anesthesiology 96:202–231, 2002.

In humans, mutations in the gene encoding the dystrophin-glycoprotein complex cause muscular dystrophy.[915] This complex is essential in maintaining the functional integrity of sarcolemma,[915][916] and dystrophic muscles are susceptible to mechanical injury as manifested by repeated necrosis and regeneration of muscle fibers.[917] Loss of dystrophin and a reduction in neuronal nitric oxide synthase in cardiac muscle have also been implicated in the pathogenesis of cardiomyopathy in these patients.[915][918][919] A reduction in neuronal nitric oxide synthase impairs regulation of the vasoconstrictor response of the affected blood vessels.[920] The distribution of muscle weakness in different types of dystrophy is shown in Figure 13-35.[921] Detailed reviews are available.[903][915][921]

Figure 13-35 Distribution of predominant muscle weakness in different types of dystrophy. **A,** Duchenne type and Becker type; **B,** Emery-Dreifuss; **C,** limb girdle; **D,** facioscapulohumeral; **E,** distal; and **F,** oculopharyngeal. *(Redrawn from Emergy AE: The muscular dystrophies. BMJ 317:991–995, 1998.)*

Duchenne's muscular dystrophy is one of the most common genetic diseases in humans, with an incidence of 1 in 3500 male births.[915] It is characterized by progressive proximal weakness beginning in early childhood and progressive cardiomyopathy.[922] Cognitive impairment is also observed and is probably caused by a lack of dystrophin in the neuronal membrane.[923] Death occurs before 30 years of age as result of respiratory or cardiac failure.[922]

Becker's muscular dystrophy is milder and affects 1 in 30,000 male births.[922] Both Duchenne's and Becker's muscular dystrophies are due to an X-linked recessive mutation in the dystrophin gene.[924] In Duchenne's muscular dystrophy, dystrophin is usually absent, whereas in Becker's muscular dystrophy, the protein is present but qualitatively and quantitatively abnormal.[904][925] Onset in childhood may occur as late as 16 years. Cardiomyopathy is present in approximately 15% of patients younger than 16 years and in 75% of those older than 40 years.[922]

Limb-girdle dystrophy is similar to Duchenne's dystrophy and is found most commonly in families in North Africa. Limb-girdle muscular dystrophy may result from autosomal dominant (type 1) or autosomal recessive (type 2) mutations and affects approximately 1 in 20,000 people.[908][915]

Congenital muscular dystrophy has the worst prognosis. Affected infants at birth have hypotonia, weakness, and respiratory and swallowing abnormalities.[909] Fukuyama-type congenital muscular dystrophy, one of the most common (0.7 to 1.2 per 10,000 births) autosomal recessive disorders in Japan, is associated with severe mental retardation and cortical dysgenesis.[926] This syndrome is caused by lesions in the fukutin gene.[910] Fukutin is a protein involved in formation of the basement membrane.[927]

Recently, it has been possible to rescue dystrophic symptoms in a mouse model of congenital muscular dystrophy by muscle-specific overexpression of an agrin minigene that replaces the missing link between the basement membrane and the muscle fiber.[928] In addition, intravenous injection of stem cells into a mouse model of congenital muscular dystrophy resulted in partial restoration of dystrophin expression in the affected muscle.[929] Therefore, these novel approaches may provide new therapeutic tools to restore muscle function in human muscular dystrophies.

Emergy-Dreifuss muscular dystrophy is characterized by early contractures of the elbows and Achilles tendons and wasting in the humeroperoneal muscles; it has an incidence of 1 in 33,000 male births. Cardiomyopathy and conduction blocks are common and can be life-threatening.[930] Two modes of inheritance exist, X-linked[906] and autosomal dominant.[907] Both forms of the disease are clinically identical.

Facioscapulohumeral muscular dystrophy is a rare variant of muscular dystrophy with an incidence of 10 to 20 cases per million.[931] It is usually manifested in late childhood as facial and scapulohumeral weakness, but cardiac involvement is generally absent. Retinal vasculopathy and sensorineural hearing loss may develop.[912][922] Oculopharyngeal dystrophy is another rare variant of muscular dystrophy that is characterized by progressive dysphagia and ptosis.

Myotonic dystrophy is the most common form of muscular dystrophy in adults, with an incidence of 1 in 8000. It can result from a mutation on either chromosome 19q13 (myotonic dystrophy type 1)[913] or chromosome 3q21 (myotonic dystrophy type 2).[914] Myotonic dystrophy type 1 is caused by a CTG expansion in the 3' untranslated region of the dystrophia myotonica-protein kinase gene (DMPK).[913][932] DMPK may be involved in cellular Ca^{2+} homeostasis.[933] Abnormalities in sarcoplasmic reticulum Ca^{2+} transport have been noted in muscle fibers with myotonic dystrophy.[934]

Myotonic dystrophy is a dominantly inherited disease characterized by myotonia, progressive myopathy, insulin resistance, defects in cardiac conduction, neuropsychiatric impairment, cataracts, testicular atrophy, and frontal balding in males.[935] Patients with myotonic dystrophy have increased mortality from respiratory complications secondary to aspiration as a result of their muscle weakness, as well as cardiac dysrhythmias. The severity of the symptoms is somewhat related to the number of trinucleotide repeats in DMPK.[936]

ANESTHETIC CONSIDERATIONS.

In dystrophic muscle, postsynaptic nAChRs are expressed as a mixture of fetal- and mature-type receptors.[17][937] Expression of fetal nAChR is not a characteristic of dystrophy but a

consequence of muscle regeneration.[937] Succinylcholine is contraindicated in these patients because of the risk of hyperkalemic cardiac arrest and rhabdomyolysis.[658][659] This response has led to a Food and Drug Administration-mandated warning against the use of succinylcholine in pediatric patients because of potential mortality in those with clinically inapparent muscular dystrophies. In addition, the incidence of malignant hyperthermia is increased in patients with muscular dystrophies.[938][939]

Resistance to nondepolarizing neuromuscular blockers would be expected on the basis of the reduced sensitivity of fetal nAChRs to competitive antagonists.[17] However, clinically the reverse is seen[940][941][942] and has been attributed to the underlying muscle wasting and reduced ability to produce contractile force.[943] Other reports, however, indicate a normal response.[944] Buzello and coauthors[945] reported that the response of patients with myotonic dystrophy to neostigmine is unpredictable.[945] Attempts to reverse residual nondepolarizing blockade in one patient with 1.0 mg neostigmine were only partially effective, and the administration of a second dose (0.5 mg) produced long-lasting muscle weakness.[945] A tonic response to neostigmine was noted in another patient with myotonic dystrophy.[945] It is advisable to avoid using anticholinesterases in these patients.

Rhabdomyolysis, with or without cardiac arrest, can occur with inhaled anesthetics, even if succinylcholine is avoided.[946][947][948] This complication raises major concern regarding the safety of inhaled anesthetics in muscular dystrophy patients.[949][950]

Mathieu and colleagues[951] identified other potential anesthetic problems in patients with myotonic dystrophies, such as glossal hypertrophy, delayed gastric emptying, contractures, spinal deformities, impaired respiratory function, and cardiomyopathy. Therefore, preoperative pulmonary and cardiac status should be evaluated carefully in these patients. The need for a cardiac pacemaker should also be assessed preoperatively in patients with high-degree atrioventricular blocks. Weak ventilatory muscles, velopalatal insufficiency, and delayed gastric emptying are expected to increase the risk of aspiration and pneumonia.[858][952][953][954] Clinical deterioration may occur in pregnancy, probably because of hormonal changes.[955] Insulin resistance syndrome is also noted in patients with myotonic dystrophy[956] and is probably the result of a lack of insulin receptors in the muscle fiber membrane.[957]

Case reports have described increased sensitivity to thiopental and propofol in myotonic dystrophy patients.[958][959][960] However, further studies have not confirmed these reports.[950][951][961] In a recent report, neither exaggerated reactions nor hemodynamic instability was observed in 13 patients with myotonic dystrophy anesthetized by continuous propofol infusion, fentanyl, atracurium, and nitrous oxide.[950] The exaggerated physiologic responses to intravenous anesthetics may be related to the severity of the disease.

Regional anesthesia and total intravenous anesthesia with propofol, opioid anesthesia, and a nondepolarizing neuromuscular blocker appear to be safe and effective anesthetic techniques in patients with muscular dystrophy.[942][950][962][963][964] It is advisable to use short-acting nondepolarizing neuromuscular blockers and monitor neuromuscular function until full recovery to avoid the administration of anticholinesterases in these patients.

Blood loss in patients with Duchenne's muscular dystrophy is significantly greater than in those with spinal muscular atrophy undergoing scoliosis surgery.[965] The difference in blood loss is probably related to an inadequate vasoconstrictive response because of a lack of dystrophin, a reduction in neuronal nitric oxide synthase, and platelet dysfunction.[919][966]

Mitochondrial Myopathies

Mitochondrial myopathies are a clinically and biochemically heterogeneous group of disorders with genetic abnormalities that involve either a mitochondrial or a nuclear gene[967]; the prevalence is 7 per 100,000.[968] This disorder targets metabolically active organs such as the liver, the brain, and skeletal muscles because they contain the largest number of mitochondria.[969][970]

Mitochondrial myopathies are often associated with abnormal proliferation of mitochondria, which accumulate beneath the sarcolemma and between muscle fibers. Histologically, staining affected muscles with Gomori modified trichrome gives the characteristic ragged red fibers. However, ragged red fibers are not pathognomonic of a mitochondrial DNA mutation.[971]

Both isolated myopathies and several multisystem syndromes have been identified. The syndromes, which are defined by characteristic clinical manifestations in addition to mitochondrial myopathy, are chronic progressive external ophthalmoplegia, including Kearns-Sayre syndrome, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes), MERRF syndrome (myoclonus epilepsy and ragged red fibers), MNGIE syndrome (myopathy, external ophthalmoplegia, neuropathy, and gastrointestinal encephalopathy), and NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa). Acquired mitochondrial myopathy has been associated with the use of zidovudine, an antiretroviral drug that depletes muscle mitochondrial DNA.[972]

ANESTHETIC CONSIDERATIONS.

Patients with mitochondrial disease may have lactic acidosis in the absence of hypoxia or sepsis.[973] Acid-base status should be monitored intraoperatively. Catecholamines, theophylline, nitroprusside, and prolonged infusion of propofol have been reported[974][975][976] to increase lactate concentrations by inducing transient abnormalities in oxidative phosphorylation.[973] Metabolic acidosis is also noted after exercise, fasting, and short-term use of a new formulation of propofol.[977] The incidence of diabetes mellitus is relatively high in patients with mitochondrial diseases.[978]

Respiratory failure may result from an impaired ventilatory response to hypercapnia and hypoxia,[979] muscle weakness,[980] diaphragmatic paralysis, or any combination of these conditions.[973] Sleep apnea is not uncommon in patients with mitochondrial disease.[981] Hypertrophic cardiomyopathies, cardiac conduction defects, and hypertension are also seen in mitochondrial disorders.[982][983] Bulbar muscle involvement is likely to increase the risk of aspiration in patients with mitochondrial disorders.[984]

Although it has been suggested that mitochondrial myopathy does not involve the neuromuscular junction,[985] increased sensitivity to different nondepolarizing

neuromuscular blockers has been demonstrated in patients with mitochondrial myopathies.[986][987] This enhanced sensitivity is of a magnitude similar to that observed in myasthenia gravis.[986] Increased sensitivity to succinylcholine was also noted in these patients.[988] The association between malignant hyperthermia and mitochondrial myopathies is not clear, but published reports indicate a possible association.[989][990][991] Intrathecal and epidural anesthesia appears to be safe in patients with mitochondrial myopathies.[992][993]

Channelopathies

Cell membranes are composed of two lipid layers, which are not permeable to ions. However, cell membranes have channels that allow ions to diffuse in order to generate an action potential.[994] Siegelbaum and Koester[995] recognized the functions of ion channels as follows: "(1) they conduct ions; (2) they recognize and select among specific ions; and (3) they open and close in response to specific electrical, mechanical or chemical signals." In the neuromuscular junction, different channels are present at the prejunctional and postjunctional sites. These channels play an integral role in maintaining the functional integrity of the neuromuscular junction in health. Disorders of channel function are called channelopathies.[996][997] Most of the channelopathies affecting skeletal muscle will be addressed here, except for malignant hyperthermia (see Chapter 29) and central core disease (for review, see Naguib and coworkers[17]).

Waxman[998] pointed out that there are three main causes of channelopathy and proposed the following classification: (1) acquired (immune mediated and toxic), (2) genetic (caused by mutations in ion channel genes[994]), and (3) transcriptional channelopathies.[998] In immune-mediated and toxic channelopathies, binding of antibodies or toxins to channels alters their function.[866] Examples of acquired (immune mediated) channelopathies affecting the neuromuscular junction are myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), and Isaacs' syndrome or neuromyotonia. A list of hereditary channelopathies that involve the neuromuscular junction is provided in Table 13-22. Waxman[998] pointed out that transcriptional channelopathies are due to "dysregulated expression of non-muted genes." Changes in Na^+ channel transcription have recently been implicated in MS.[999]

Table 13-22 -- Channelopathies in neuromuscular diseases

Disease	Ion Channel Subunit	Gene	Reference
Myotonia congenita (dominant and recessive)	Voltage-gated Cl^- channel	*CLCN1*	[1000]
			[1001]
Hyperkalemic periodic paralysis	Voltage-gated Na^+ channel	*SCN4A*	[1002]
Paramyotonia congenita			[1003]
Potassium-aggravated myotonia			[1004]
Hypokalemic periodic paralysis	Voltage-gated Ca^{2+} channel	*CACNA1S*	[1005]

Disease	Ion Channel Subunit	Gene	Reference
type 1	(dihydropyridine receptor)		
Hypokalemic periodic paralysis type 2	Voltage-gated Na^+ channel	*SCN4A*	[1006]
Malignant hyperthermia	Ligand-gated Ca^{2+} channel	*RYR1*	[1007]
Central core disease			[1008]
Congenital myasthenic syndromes	nAChR channel	*CHRNA1*	[1009]
X-linked Charcot-Marie-Tooth disease	Connexin	*GJB1 (Cx32)*	[882]
nAChR, nicotinic acetylcholine receptor.			

Modified from Naguib M, Flood P, McArdle JJ, et al: Advances in neurobiology of the neuromuscular junction: Implications for the anesthesiologist. Anesthesiology 96:202–231, 2002.

The Role of Ion Channels in Neuromuscular Transmission

For a more extensive account of this subject, the reader is referred to reviews by Hoffman,[1010] Cooper and Jan,[1011] Lehmann-Horn and Jurkat-Rott,[1012] and Kleopa and Barchi.[1013] Based on the current evidence,[1010][1011][1012][1014] the role of ion channels in neuromuscular transmission can be summarized as follows:

1. Motor nerve:
    a. Depolarization of the motor nerve will open the voltage-gated Ca^{2+} channels that trigger both mobilization of synaptic vesicles and the fusion machinery in the nerve terminal to release acetylcholine.
    b. Several forms of K^+ channel present in the nerve terminal serve to limit the extent of Ca^{2+} entry and transmitter release (i.e., initiate repolarization of the nerve terminal).[1011]
2. Muscle:
    a. The released acetylcholine binds to α-subunits of the nAChRs. These ligand-gated cation channels allow sodium to enter and depolarize the muscle cell membrane at the neuromuscular junction.[997][1011]
    b. This depolarization activates voltage-gated sodium channels, which mediate the initiation and propagation of action potentials across the surface of the muscle membrane and into the transverse tubules (T-tubules) and thereby result in upstroke of the action potential.[997][1011][1012]
    c. Two types of calcium channels are recognized: the dihydropyridine receptor (DHPR) in the T-tubules and the ryanodine receptor (RyR1) in the sarcoplasmic reticulum (Fig. 13-36). DHPRs act as "voltage

sensors,"[1015][1016] are activated by membrane depolarization, and in turn activate RyR1 receptors.

d. DHPR-RyR1 interaction[1017] releases large amounts of Ca^{2+} from the sarcoplasmic reticulum, which causes muscle contraction. This process is known as excitation-contraction coupling.[1010]

e. Repolarization of the muscle membrane is initiated by closing of the sodium channels and by opening of the potassium ion channels that conduct an outward K^+ current.[1014]

f. Return the muscle membrane potential to its resting level (approximately -70 to -90 mV) is achieved by allowing Cl^- to enter the cell through voltage-sensitive chloride channels.[1011]

A list of ion channels mutated in human neuromuscular disease is presented in Table 13-22.

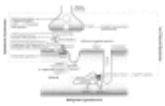

Figure 13-36 Disorders of channel function (channelopathies) that cause myasthenic syndromes, myotonias, malignant hyperthermia (MH), and central core disease (CCD). AChE, acetylcholinesterase; DHP receptor, dihydropyridine receptor; MuSk, muscle-specific kinase; nAChR, nicotinic acetylcholine receptor; RyR, ryanodine receptor; SV, synaptic vesicle; VGCC (P/Q), voltage-gated calcium channel (P/Q type); VGCLC, voltage-gated chloride channel; VGKC, voltage-gated potassium channel; VGNC, voltage-gated sodium channel.

Myasthenic Syndromes

The large number (10,000/μm^2) of nAChRs in the postsynaptic muscle membrane is crucial for maintaining normal neuromuscular function and for allowing a margin of safety in neuromuscular transmission.[1018] Although it is now established that MG is due to autoantibodies to nAChRs, several other autoimmune and genetic myasthenic syndromes have been identified (Fig. 13-36 and Table 13-23).[998] For more extensive accounts, see Vincent and colleagues,[1018][1019] Lindstrom,[1020] and Drachman.[1021]

Table 13-23 -- Myasthenic syndromes

Syndrome	Location	Mechanism	Etiology
Lambert-Eaton myasthenic syndrome	Presynaptic	Autoimmune	Antibodies to voltage-gated calcium channels at the motor nerve terminal
Congenital myasthenic syndromes		Genetic	
Choline acetyltransferase deficiency	Presynaptic		Mutations in choline acetyltransferase
Acetylcholinesterase	Synaptic		Mutations in the gene encoding the

Syndrome	Location	Mechanism	Etiology
deficiency			collagenic tail subunit (ColQ) of the enzyme that anchors acetylcholinesterase in the synaptic cleft
Slow- and fast-channel syndromes	Postsynaptic		Mutations in nAChR genes
nAChR deficiency	Postsynaptic		Mutations in nAChR genes or in rapsyn
Myasthenia gravis	Postsynaptic	Autoimmune	
Seropositive			Antibodies to nAChRs
Seronegative			Antibodies to MuSK
MuSK, muscle-specific kinase; nAChR, nicotinic acetylcholine receptor.			

Myasthenia Gravis

MG is an antibody-mediated autoimmune disease targeted against the α-subunit of nAChRs at the neuromuscular junction; it has a prevalence of 0.25 to 2.00 per 100,000 people.[1018][1019][1020][1021] In MG, the number of functional nAChRs is markedly decreased as a result of (1) cross-linking of antibodies to the receptors[1022] and (2) focal membrane lysis caused by complement fixation.[1021][1023][1024] The condition results in muscular weakness and fatigability.[1021]

Antibodies to the nAChR are present in about 80% of patients with MG.[1025][1026] In the remaining 20% of patients (called seronegative patients), nAChR antibodies are not detectable.[1027] Recently, another form of antibodies has been identified in seronegative MG patients. In about 70% of seronegative (but not seropositive) MG patients, the muscle-specific receptor tyrosine kinase (MuSK) has been identified as the target for autoantibodies (see Fig. 13-36).[1028] MuSK mediates the agrin-induced clustering of AChRs during synapse formation and is also expressed at the mature neuromuscular junction.[17][1029] Interestingly, antibodies from MG patients do not cross-react with the α_3-subunit of the nAChR that is found principally in the autonomic nervous system or the $\alpha_4\beta_2$ nAChRs that occur in the CNS. Perhaps this explains the lack of autonomic and CNS symptoms in typical MG.[1030]

The triggers for the immune response in MG are largely unknown. The thymus has been implicated because approximately 70% of MG patients have thymic lymphoid follicular hyperplasia with germinal centers that produce antibodies to nAChRs.[1020] In a small percentage of MG patients, autoantibodies develop as part of a paraneoplastic syndrome.[1020] About 12% of patients with MG have a thymoma, whereas 30% to 50% of patients with a thymoma suffer from MG.[1020] It is believed that antibodies to nAChRs are produced in other locations because thymectomy does not cure MG and does not protect against the occurrence of MG.[1020][1031] Fetal-type nAChRs, which are normally expressed in extraocular muscles, may be immunogenic as shown by their involvement in MG.[1020]

Some evidence also indicates that antibodies generated in response to microbial antigens may be a trigger for MG in certain patients.[1032]

Electron microscopic studies show that the postsynaptic membrane has a simplified appearance with little folds[1033] associated with a marked reduction in the clustering of nAChRs to approximately 30% of those seen in normal neuromuscular junctions.[1040] Although acetylcholine sensitivity is reduced, a compensatory increase in the release of acetylcholine occurs at the neuromuscular junction in both experimental models of MG[1034] and muscle biopsy specimens from patients with MG.[1035]

Improvement in strength after the intravenous injection of edrophonium (Tensilon) helps confirm the diagnosis of MG. After a test dose of 1 to 2 mg, a total dose of 10 mg is administered intravenously. A positive response is expected within 5 minutes. No specific immunotherapy is available for MG. Nonspecific immunosuppression with steroids and other drugs and plasmapheresis are often combined with thymectomy and symptomatic treatment with anticholinesterases.

Lambert-Eaton Myasthenic Syndrome

LEMS is an example of an acquired (immune mediated) channelopathy that results from autoantibodies targeting the presynaptic voltage-gated Ca^{2+} channels and possibly another presynaptic component (such as synaptotagmin), and as a consequence, acetylcholine release is reduced.[1026][1036][1037][1038] Synaptotagmin plays an important role in synaptic vesicle fusion and fast release of acetylcholine.[17][1039] Approximately 60% of LEMS patients show a paraneoplastic response, often in association with small cell carcinoma of the lung.[1026] LEMS is also characterized by weakness and fatigability.

Although both LEMS and MG are autoimmune diseases, they have several differences: (1) in LEMS, the presynaptic site of the neuromuscular junction is the target for autoantibodies, whereas postsynaptic nAChRs are the target in MG; (2) autonomic disturbances are seen in about 30% of patients with LEMS but not in patients with MG; (3) unlike MG, anticholinesterases are of little therapeutic value in LEMS[1036]; (4) improvement in muscle strength is seen after exercise in LEMS as a result of summation of presynaptic Ca^{2+} signals and improved acetylcholine release,[1040] but in MG improvement occurs after rest; (5) LEMS is differentiated from MG by electromyography, in which facilitation of the electromyographic response, rather than fade, occurs during high-frequency (30 to 50 Hz) stimulation; and (6) the two diseases can also be differentiated by antibody titer to specific channels. The acetylcholine contents and the architecture of the neuromuscular junction are normal in diseased nerve endings in LEMS.

Plasmapheresis or intravenous immunoglobulin can often give transient improvement in LEMS.[1041] Treatment with 3,4-diaminopyridine results in significant improvement in symptoms in patients with LEMS.[1042] Pyridostigmine potentiates the response to 3,4-diaminopyridine in many patients.[1042] 3,4-Diaminopyridine blocks potassium channels and thereby prevents potassium efflux. Prevention of potassium efflux increases the action potential duration, which in turn prolongs the activation of voltage-gated Ca^{2+} channels,

along with a concomitant increase in intracellular Ca^{2+} concentration and acetylcholine release.

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMSs) are diverse disorders characterized by muscle weaknesses and fatigability (like MG) and caused by congenital defects in different components of the neuromuscular junction (see Fig. 13-36).[994][1043][1044][1045] Inherited mutations are seen in the presynaptic (synaptic vesicles, choline acetyltransferase), synaptic (acetylcholinesterase), or postsynaptic (nAChRs or rapsyn) component of the neuromuscular junction.[1009][1020][1044][1045][1046][1047][1048][1049] These mutations result in either increasing (gain of function) or decreasing (loss of function) magnitude of response to acetylcholine.[1044] Inheritance of CMSs is either autosomal dominant or autosomal recessive. The most frequent type of postsynaptic CMS is the slow-channel syndrome.[1009][1020][1046][1047][1048][1049] Mutations in the α-, β-, and most frequently the ϵ-subunit of nAChRs cause slow-channel congenital myasthenic syndromes (SCCMSs).[17] SCCMSs typically show dominant inheritance.

MG and CMSs have several differences: (1) unlike MG, antibodies against the nAChRs are not present and immunosuppressive therapy is not effective in CMSs, and (2) in contrast to neonatal MG, which is caused by passive transfer of anti-nAChR antibodies from a myasthenic mother to the fetus, the mother of a CMS patient does not have myasthenia.

An increase in the affinity of the nAChR for acetylcholine is seen in SCCMSs.[1009] The net effect of such gain-of-function mutations is to prolong the open state of the nAChR.[17] Such prolongation allows what is normally physiologic activation of the neuromuscular junction to overload the postsynaptic region with Ca^{2+} and initiates necrosis.[17] Activation of nitric oxide synthase at the neuromuscular junction can also contribute to free radical damage of the end plate. Nitric oxide synthase inhibitors may be of value in these patients.[1050] Patients with SCCMSs are significantly improved by quinidine sulfate because it normalizes the open duration of slow-channel mutants.[1051]

Loss-of-function mutations, seen in the α- and ϵ-subunits, decrease the rate of channel opening and increase the closure rate.[1052][1053] This loss of nAChR function reduces the safety factor for synaptic transmission.[17]

ANESTHETIC CONSIDERATIONS.

For detailed reviews, see Baraka[1054] and Abel and Eisenkraft.[1055] Preoperative assessment and preparation of an MG patient should include (1) consultation with the patient's neurologist to learn of the recent history and progress of management; (2) preoperative drug therapy (such as pyridostigmine and immunosuppression drugs) and the potential impact of this drug therapy on responses to neuromuscular blockers; (3) counseling and preparation of the patient for possible postoperative endotracheal intubation and mechanical ventilation; and (4) optimization of medical management for myasthenia, which may include preoperative plasmapheresis and continuation of the anticholinesterase therapy. Pyridostigmine therapy should be continued preoperatively.

Patients with bulbar involvement are at increased risk for respiratory depression and aspiration, especially during myasthenic crises.[1056] It has been reported that 25% of myasthenic crisis episodes were associated with radiographic evidence of aspiration pneumonia.[1057] About 33% of the patients in crisis had severe oropharyngeal weakness.[1057] Pulmonary function tests, including flow-volume loops, may be necessary to predict the need for mechanical ventilation postoperatively.[1058]

Because of the decreased number of nAChRs, myasthenic patients are resistant to succinylcholine (Fig. 13-37).[1059] On the other hand, butyrylcholinesterase activity may be decreased in myasthenic patients by preoperative plasmapheresis or by the administration of pyridostigmine (or by both), which would result in potentiation of succinylcholine[1060] or mivacurium-induced blockade.[1061] The interplay between these two factors (resistance to succinylcholine versus reduction in butyrylcholinesterase activity) should be considered when administering succinylcholine to patients with MG (Fig. 13-38). In addition, progression to a phase 2 block is not uncommon in these patients.[1062] Succinylcholine should be avoided in patients with SCCMSs because succinylcholine would be expected to worsen the existent state of excitotoxicity.[17]

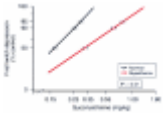

Figure 13-37 Succinylcholine dose-response curves in normal and myasthenic patients. *(Redrawn from Eisenkraft JB, Book WJ, Mann SM, et al: Resistance to succinylcholine in myasthenia gravis: A dose-response study. Anesthesiology 69:760–763, 1988.)*

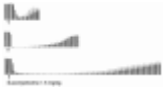

Figure 13-38 Electromyographic response to ulnar nerve stimulation by train-of-four stimulation every 20 seconds. Shown is the effect of 1.5 mg/kg succinylcholine in three myasthenic patients with differing butyrylcholinesterase activity. *Upper tracing,* butyrylcholinesterase = 5.16 U/mL; *middle tracing,* butyrylcholinesterase = 1.45 U/mL; *lower tracing,* butyrylcholinesterase = 0.73 U/mL. *(From Baraka A: Suxamethonium block in the myasthenic patient. Correlation with plasma cholinesterase. Anaesthesia 47:217–219, 1992.)*

The loss of approximately 70% of the postsynaptic nAChRs means that myasthenic patients have a marked reduction or even total loss of the safety margin for neuromuscular transmission. Therefore, it is not unexpected that patients with MG are extremely sensitive to nondepolarizing neuromuscular blockers (Fig. 13-39 and Fig. 13-40).[1054][1063][1064][1065] The effective dose of vecuronium is 250% greater in control patients than in MG patients,[1066] but this does not mean that nondepolarizing neuromuscular blockers are contraindicated in these patients. With careful titration and adequate monitoring of neuromuscular function, nondepolarizing agents have been used safely in myasthenic patients undergoing thymectomy.[1054][1058][1063][1064] Long-acting neuromuscular blocking drugs should be avoided in these patients. Intermediate-acting drugs should be used in low dosage as guided by monitoring with a nerve stimulator. About one tenth to one fifth the ED_{95} should be given as a test dose to estimate the patient's requirement. Individual

response will vary from extreme sensitivity, such that the test dose is all that is needed, to nearly normal relaxant requirements.

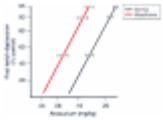

Figure 13-39 Cumulative dose response for atracurium in patients with myasthenia gravis. *(Redrawn from Smith CE, Donati F, Bevan DR: Cumulative dose-response curves for atracurium in patients with myasthenia gravis. Can J Anaesth 36:402–406, 1989.)*

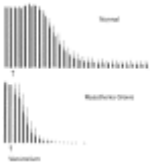

Figure 13-40 Electromyographic response to ulnar nerve stimulation. Injection of 0.1 mg/kg vecuronium in a normal patient resulted in a slow onset of nondepolarizing block *(upper trace)*, whereas injecting one tenth the dose (0.01 mg/kg vecuronium) to a myasthenic patient resulted in a rapid onset of block *(lower trace)*.
(From Baraka A: Onset of neuromuscular block in myasthenic patients. Br J Anaesth 69:227–228, 1992.)

Pyridostigmine will modify the response to relaxants as follows: (1) the sensitivity to nondepolarizers will be diminished, (2) the response to succinylcholine or mivacurium may be prolonged, and (3) reversal of residual block at the end of the procedure may be ineffective because much acetylcholinesterase inhibition already exists as a result of chronic pyridostigmine therapy. Prolonged depolarizing blockade has been documented after reversal of vecuronium with neostigmine (3 mg) was attempted in a myasthenic patient.[1067] Consequently, it may be safer to allow spontaneous recovery from relaxation postoperatively while continuing supportive mechanical ventilation. Atracurium and cisatracurium appear to be the preferred muscle relaxants in myasthenia because their metabolism can obviate the need for reversal.

Different anesthetic techniques have been used in myasthenic patients. Although surgical relaxation can be provided for a myasthenic patient with only a potent inhaled anesthetic without neuromuscular blockers, this technique may be associated with slow recovery from anesthesia. In addition, myasthenic patients are more sensitive than normal to the neuromuscular depressant effects of halothane and isoflurane.[1068][1069][1070] Therefore, it may be safer to intubate the trachea and provide surgical relaxation with the aid of nondepolarizing neuromuscular blockers in these patients than to use deep inhalation anesthesia.

A thoracic epidural anesthetic in combination with balanced general anesthesia provides excellent analgesia both intraoperatively and during the period after transsternal thymectomy.[1071] Regional anesthesia was also used successfully to provide labor analgesia with minimal muscle weakness in a parturient with MG.[1072] However, regional anesthesia is not a risk-free alternative.[1073]

Patients with LEMS are sensitive to both depolarizing and nondepolarizing neuromuscular blockers.[1074] In fact, patients with LEMS have significantly greater sensitivity to nondepolarizing neuromuscular blockers than those with MG do.[1075] In patients with

LEMS, neostigmine is ineffective as an antagonist for residual neuromuscular block.[1076] It has been suggested that a combination of an anticholinesterase and 4-aminopyridine might be of value in these patients.[1076] Oral 3,4-diaminopyridine should be continued after surgery. The bulbar muscles are usually spared in LEMS patients, but partial weakness and paralysis are not uncommon during recovery from general anesthesia in these patients.[1056]

All myasthenic patients should be closely monitored for neuromuscular weakness postoperatively in the surgical ICU. The differential diagnosis of postoperative weakness in myasthenic patients should include residual effects of neuromuscular blockers or anesthetic drugs, drugs that interfere with neuromuscular transmission (such as aminoglycoside antibiotics, antiarrhythmics, and psychotropics), and myasthenic or cholinergic crisis.

Ion Channel Myotonias

Myotonias are currently differentiated into two different types of disorders. The first type consists of channelopathies (Fig. 13-36 and Table 13-24; also see Table 13-22) and includes acquired neuromyotonia, myotonia congenita, paramyotonia, hyperkalemic periodic paralysis, potassium-aggravated myotonia, and hypokalemic periodic paralysis. The latter is a muscle ion channel disorder without myotonia. The second type includes myotonic dystrophy (see the section "Muscular Dystrophies").

Table 13-24 -- Clinical features of ion channel disorders causing myotonia

	Autosomal Dominant Myotonia Congenita (Thomsen)	Autosomal Recessive Myotonia Congenita (Becker)	Potassium-Aggravated Myotonia	Paramyotonia Congenita	Hyperkalemic Periodic Paralysis (HyperPP)	Hypokalemic Periodic Paralysis (HypoPP)
Age at onset	Infancy-early childhood	Late childhood (variable)	First or second decade	First decade	First decade	Second decade (variable)
Initial symptoms	Muscle hypertrophy and generalized myotonia; occasional asymptomatic patients with electrical myotonia	Muscle hypertrophy (legs), generalized myotonia, transient weakness after rest	Myotonia (fluctuans, permanens, painful) affecting facial, eyelid, and paraspinal muscles	Paradoxical eyelid and grip myotonia; focal paralysis common, may overlap with HyperPP	Brief (<1 hr) paralytic attacks; myotonia or paramyotonia (eyelids) between paralytic episodes	Paralytic episodes that last hours-days, tend to remit with age, affect men more than women; no myotonia
Provocative stimuli	Myotonia worsened by rest,	Myotonia worsened by rest or	Potassium, cold, infection,	Exercise and cold	Rest after exercise; cold and	Rest after exercise, often when waking up

	Autosomal Dominant Myotonia Congenita (Thomsen)	Autosomal Recessive Myotonia Congenita (Becker)	Potassium-Aggravated Myotonia	Paramyotonia Congenita	Hyperkalemic Periodic Paralysis (HyperPP)	Hypokalemic Periodic Paralysis (HypoPP)
	improves with exercise ("warm-up" phenomenon)	maintenance of same posture ("warm-up")	exercise		potassium trigger both paralysis and myotonia	in the morning, after carbohydrate-rich and salty meals
Myopathy	Weakness may develop in older age; biopsy shows mild abnormalities	Possible muscle atrophy and weakness late in life	Rare myopathy, muscle hypertrophy common	Very rare	Infrequent	Possible progressive myopathy (vacuolar in HypoPP-1, tubular aggregates in HypoPP-2)
Therapy	Exercise, antimyotonia therapy (phenytoin, mexiletine)	Exercise, antimyotonia therapy	Acetazolamide, mexiletine, low-potassium diet, flecainide in painful variant	Mild exercise; avoid exposure to cold, mexiletine	Prevention with thiazide diuretics, acetazolamide, sodium restriction, carbohydrate-rich meals; attacks treated with diuretics, calcium gluconate	Prevention with potassium supplements, acetazolamide (worsens HypoPP-2), dichlorophenamide; attacks treated with oral potassium

From Kleopa KA, Barchi RL: Genetic disorders of neuromuscular ion channels. Muscle Nerve 26:299–325, 2002.

Acquired Neuromyotonia

Neuromyotonia, also known as Isaacs' syndrome or continuous muscle fiber activity syndrome, is a rare peripheral motor neuron disorder. Like MG and LEMS, neuromyotonia is another example of an acquired (immune mediated) channelopathy.[1077][1078][1079] It is believed that autoantibodies target the presynaptic voltage-gated potassium channels (see Fig. 13-36), thereby inhibiting action potential repolarization, enhancing transmitter release,

and inducing hyperexcitability.[1026][1077] These antibodies have been detected in neuromyotonia patients.

In contrast to the weaknesses and fatigability seen in MG or LEMS, neuromyotonia is associated with increased activity at the neuromuscular junction that results in severe muscle cramps, stiffness, weakness, and often myokymia (muscular twitching during rest).[1026] Some patients exhibit CNS symptoms such as insomnia, mood changes, and hallucinations.[1077] The association of neuromyotonia with the aforementioned CNS manifestations has been coined "Morvan's syndrome."[1080] A paraneoplastic response often in association with small cell carcinoma or thymoma is seen in about 20% of patients with neuromyotonia.[1081][1082] Neuromyotonia can coexist with MG.[1018]

Drugs that act by increasing the sodium-pumping action of nerve and muscle tissue, such as phenytoin, are effective in treating neuromyotonia.[1083] Plasmapheresis can provide both clinical and electromyographic improvement.[1084] Immunosuppressive therapy with azathioprine may be helpful in severe cases.

ANESTHETIC CONSIDERATIONS.

Spinal and epidural anesthesia, as well as succinylcholine and nondepolarizing neuromuscular blockers, are effective in abolishing spontaneous discharge and producing muscle relaxation.[1085][1086] Peripheral nerve blocks are not effective in abolishing myokymia in all patients,[1086] thus suggesting that in some cases the hyperexcitability originates within the distal nerve trunk.[1079] It should be noted that the abnormal muscle fiber activity can persist during sleep and general anesthesia.

Epidural anesthesia was used successfully for labor and delivery in a patient with neuromyotonia.[1087] The clinical effects of general anesthetics and neuromuscular blockers have not yet been reported in these patients. However, resistance to nondepolarizing neuromuscular blockers is expected in neuromyotonia because of (1) the increased acetylcholine release in these patients[1088] and (2) in vitro evidence of resistance of dTc.[1089] Some patients with acquired neuromyotonia may have autonomic and sensory neuropathies.[1077]

Myotonia Congenita

Both dominant (Thomsen) and recessive (Becker) forms of myotonia congenita are caused by mutations in the gene encoding the skeletal muscle voltage-gated chloride channel,[1000][1001][1090] with an estimated prevalence of 1 in 23,000 for recessive myotonia and 1 in 50,000 for dominant myotonia.[1013] As discussed before (see the section "The Role of Ion Channels in Neuromuscular Transmission"), chloride channels are responsible for return of the membrane potential to its resting level.[1011] Mutations in this channel decrease Cl^- conductance into the cell and thereby lead to hyperexcitability of the muscle membrane and muscle stiffness (see Fig. 13-36).[1010][1011][1091] Myotonias are characterized by difficulty initiating muscle movement and delayed muscle relaxation after voluntary contraction. It improves with sustained activity (warm-up phenomenon).

Muscle stiffness responds to Na^+ channels blockers such as local anesthetics and antiarrhythmic drugs.[1091] Although these drugs do not affect the kinetics of Cl^- channels, they decrease cell-membrane excitability.[1092]

ANESTHETIC CONSIDERATIONS.

Myotonia may be precipitated by cold, shivering, diathermy, succinylcholine, and anticholinesterases (see Table 13-24).[945][1013][1092] The association between myotonia and malignant hyperthermia is uncertain, probably because of the difficulty in interpretation of the caffeine-halothane contracture test in myotonic patients.[1093][1094] It is prudent, however, to avoid all anesthetic triggering agents in these patients.

Myotonia developing in response to direct surgical activation of muscle is difficult to prevent and treat.[1095] Unlike local anesthetics and antiarrhythmic drugs, nondepolarizing neuromuscular blockers are not effective in alleviating this myotonic response.[1091] Clinical deterioration may occur in pregnancy and is probably due to the associated hormonal changes. Epidural anesthesia is reported to be safe in these patients.[1096]

Hyperkalemic Periodic Paralysis, Paramyotonia Congenita, and Potassium-Aggravated Myotonia

Mutations in the skeletal muscle voltage-gated Na^+ channel gene produce the clinical phenotypes of hyperkalemic periodic paralysis (HyperPP), paramyotonia congenita, and potassium-aggravated myotonia (see Fig. 13-36).[1002][1012] As discussed before (see the section "The Role of Ion Channels in Neuromuscular Transmission"), voltage-gated sodium channels are responsible for amplification and propagation of action potentials along the muscle membrane. Mutant channels exhibit sustained Na^+ currents that lead to prolonged membrane depolarization causing myotonia, followed by membrane desensitization (or inactivation) resulting in paralysis.[1010][1011][1012][1013][1097] This is another example of a gain-of-function mutation.

HyperPP is a rare autosomal dominant disorder with a prevalence of 1:100,000.[1012] It is characterized by episodes of muscle weakness associated with hyperkalemia and with signs of myotonia in the interval between attacks.[1010] Respiratory and cardiac muscles are not affected, probably because of the existence of Na^+ channels in these muscles different from those expressed in skeletal muscle.[1013] The attacks of paralysis are frequent, brief, and often precipitated by rest after exertion, stress, ingestion of foods with high potassium content such as bananas, or the administration of potassium. A cold environment, emotional stress, and pregnancy provoke or worsen the attacks.[1014] Increases in serum K^+ up to 5 to 6 mmol/L may be seen during the attack.[1013] Prophylactic treatment with potassium-wasting diuretics can attenuate the frequency and severity of attacks.

The clinical manifestations of HyperPP, paramyotonia congenita, and potassium-aggravated myotonia are similar, which suggest that the three disorders may be allelic (i.e., a single genetic defect is responsible for coinheritance).[1003][1004][1098][1099] Normokalemic periodic paralysis is a variant of HyperPP and has been reported in only a few families.[1100][1101][1102]

ANESTHETIC CONSIDERATIONS.

Potassium depletion before surgery, maintenance of carbohydrate stores with dextrose-rich, potassium-free intravenous solutions, maintenance of normothermia, and avoidance of acidosis are essential in the anesthetic management of these patients.[1013][1103] Prewashed packed red blood cells should be used if blood transfusion is required. Careful and frequent monitoring of plasma potassium concentrations and acid-base status is of greatest importance. Succinylcholine should be avoided because it will result in increases in serum potassium concentrations and can cause myotonic symptoms in these patients.[1104] Anticholinesterase drugs should be avoided as well because they may provoke a myotonic reaction.[1105]

An association between malignant hyperthermia and HyperPP in the adult skeletal muscle sodium channel gene has been established.[1106] Patients with HyperPP appear to have a normal response to nondepolarizing neuromuscular blockers.[1103] Hyperkalemia should be considered in the differential diagnosis of postoperative residual weakness. Hyperkalemia should be treated with immediate hyperventilation, calcium chloride, 1.0 to 2.0 mg intravenously, sodium bicarbonate, 1 mEq/kg, and intravenous glucose and insulin (10 U regular insulin in 50 mL 50% glucose or, for children, 0.15 U regular insulin per kilogram in 1.0 mL/kg 50% glucose). Propofol was shown to target and block both normal and mutant voltage-gated sodium channels in a concentration- and voltage-dependent manner.[1107][1108] Therefore, propofol might be beneficial. Spinal anesthesia is reported to be a safe alternative to general anesthesia in these patients.[1109] Cardiac anesthesia poses particular problems. During recovery, special attention should be directed at maintaining normal body temperature and electrolyte and acid-base status.

Hypokalemic Periodic Paralysis

Mutations in the skeletal muscle voltage-gated Ca^{2+} channel gene (DHPR) produce hypokalemic periodic paralysis type 1 (HypoPP-1).[1005] HypoPP-2 is caused by mutations in the gene encoding the voltage-gated Na^{+} channel of skeletal muscle (see Fig. 13-36).[1097][1098] Both types have the same clinical features.

HypoPP is a rare autosomal dominant disorder with a prevalence of 1:100,000.[1012] It is characterized by episodic weakness associated with hypokalemia during attacks.[1014] The hypokalemia has been attributed to increased activity of the Na^{+}-K^{+} pump by insulin, which results in shifting of K^{+} from the extracellular space into the intracellular compartment.[1111][1112] As discussed before (see the section "The Role of Ion Channels in Neuromuscular Transmission"), repolarization of the membrane in normal muscle is initiated by the outward K^{+} current through the potassium ion channel.[1014] The abnormal inward shifting of K^{+} (into the cell) in HypoPP causes prolonged depolarization leading to inactivation of both the mutant sodium channels in HypoPP-2 and normal sodium channels and thereby results in muscle weakness and paralysis.[1006][1013][1113][1114] Although this description does not include an explicit role for Ca^{2+} ion channels, the intracellular Ca^{2+} concentration is essential in regulating insulin secretion,[1115][1116] and it appears that mutations of the Ca^{2+} channel in HypoPP-1 may alter this mechanism.[1013][1112] HypoPP is an example of a loss-of-function mutation of Na^{+} and Ca^{2+} ion channels.[1014]

In contrast to HyperPP, myotonia is absent in HypoPP, and ventricular dysrhythmias may occur during hypokalemic attacks.[997] HypoPP attacks are triggered by hypothermia, carbohydrate-rich meals, insulin, and vigorous exercise and can be treated by potassium administration (see Table 13-24).[1013] Prophylactic treatment with acetazolamide (a carbonic anhydrase inhibitor) is successful in HypoPP-1 patients, perhaps by producing metabolic acidosis, which decreases the urinary excretion of K^+.[1117] However, acetazolamide should not be used in HypoPP-2 patients because it can induce attacks of weakness and paralysis in this group of patients.[1110]

ANESTHETIC CONSIDERATIONS.

Preoperative stress should be adequately alleviated by the administration of anxiolytic drugs such as benzodiazepines. Frequent monitoring of plasma potassium concentrations and acid-base status is required.

A normal response to succinylcholine is noted in these patients,[1118] but an association between HypoPP and malignant hyperthermia has been reported.[1119] There are no reports in the literature on the effects of nondepolarizing neuromuscular blockers in these patients, and their use seem to be safe in HypoPP patients.[1118] In a review of 21 anesthetics administered to members of a family with HypoPP, seven patients suffered from mild or severe post-operative paralysis.[1120] Hypokalemia should be considered in the differential diagnosis of postoperative residual weakness.

Spinal anesthesia and epidural anesthesia are safe alternatives to general anesthesia in these patients.[1121] It should be noted, however, that epidural,[1122] axillary, and intercostal nerve blocks[1123] lower serum potassium 0.3 to 0.7 mmol/L on average. Administration of epinephrine with the local anesthetic accounts for a proportion of this decline.[1122]

ECONOMICS AND OUTCOME IN PRACTICE WITH NEUROMUSCULAR BLOCKING DRUGS

Although the introduction of neuromuscular blocking drugs with intermediate and short durations of action has significantly changed the practice of providing neuromuscular blockade, the acquisition cost of these drugs is considerably greater than that of long-acting drugs such as pancuronium. In recent years, there has been pressure to reduce health care costs by reverting to more widespread use of long-acting neuromuscular blockers.[1124][1125] It is appropriate to remember that the acquisition cost of anesthesia drugs is likely to amount to approximately 0.25% of the total hospital budget and is only a fraction of the cost of running an operating room.[263] Focusing on only drug acquisition costs while trying to reduce health care costs is a simplistic view,[1126] and the impact of the choice of neuromuscular blocker on patient outcome must also be considered. Outcomes that result in increased medical cost must also be included in a patient's total health care costs.[1127]

A prospective trial of anesthesiologists' practices demonstrated that anesthesiologists are not inclined to choose medications based on price alone.[1128] However, price labeling, associated with education regarding the cost of medications in another study, did reduce the cost of acquisition of neuromuscular blockers by 12.5% over a 12-month period. This reduction translated into a savings of just over $47,000.[1129] The decrease in expenses for

neuromuscular blockers was accomplished by a 104% increase in the use of pancuronium. However, unless the educational programs are ongoing and the staff remains well motivated, cost savings from this type of practice modification are short lived.[1130]

If a reduction in drug acquisition costs is to be considered an appropriate means of decreasing health care cost, anesthesiologists may look at their own practices. A year-long survey was performed in one hospital for waste of six frequently used or expensive medications. These drugs included thiopental, succinylcholine, rocuronium, atracurium, midazolam, and propofol. The study demonstrated that the total cost of drugs drawn up but not administered amounted to more than $165,000.[1131] Waste of thiopental and propofol accounted for most of this expense. In this practice, rocuronium and atracurium each accounted for 2% of the total expense. Succinylcholine did not significantly contribute to the cost of drug wastage. Although efficiency in the dosing of neuromuscular blockers can be improved, decreasing the amount of neuromuscular blockers drawn up and not administered to patients may not be a truly significant way to decrease health care costs.

The adequacy of recovery of neuromuscular function is crucial because even minor degrees of residual neuromuscular blockade have significant adverse effects.[53][54][563][565] The muscles of airway protection are very sensitive to residual block,[53] and this predisposes patients to pulmonary aspiration.[563] In addition, residual neuromuscular blockade may compromise a patient's "street readiness" in the postoperative recovery period.[54] Mounting evidence indicates that the standard for acceptable recovery of neuromuscular function is no longer a TOF ratio of 0.7, but in fact greater safety might be achieved at 0.9.[54][563]

The relative incidence of residual neuromuscular blockade in the postoperative period is greater with neuromuscular blockers that have a longer duration of action. In 1979, a study by Viby-Mogensen and colleagues[58] showed that the incidence of residual weakness in the recovery room was higher than 40%. At that time, only long-acting drugs were available. With the introduction of vecuronium and atracurium, the incidence of residual weakness declined significantly to less than 10%.[59] If, however, a TOF ratio of 0.9 is to now be considered adequate, the incidence of unacceptable levels of neuromuscular block on admission to the PACU may be higher.[55]

Residual neuromuscular blockade caused by the administration of long-acting nondepolarizing neuromuscular blockers appears to predispose patients to a greater risk of postoperative pulmonary complications.[60] These complications constitute the greatest potential added expenses, and they accrue as a result of the choice of long-acting neuromuscular blockers over shorter-acting drugs. Delayed discharge from the PACU[1132] also has a significant cost impact. The increased length of stay in the PACU because of long-acting neuromuscular blockers has an estimated cost penalty to the institution of $40 per patient.[1132]

It is argued that the use of long-acting neuromuscular blockers is without adverse effect if strict practice guidelines regarding their use and dosing are implemented and continuously enforced.[1133][1134] However, even with strict regulation, the use of pancuronium rather than an intermediate-acting neuromuscular blocker is associated with a delay (a mean of 3

minutes) in the time from the end of the surgical procedure until the patient reaches the PACU. Much debate has been generated about the importance of this 3-minute delay.

The risks of residual weakness associated with the use of long-acting neuromuscular blockers apply to situations in which the patient's trachea will be extubated at the end of the surgical procedure. After cardiac surgery, for instance, where the tracheal tube will remain in place and the patient's ventilation will be supported postoperatively for hours or days, the use of long-acting neuromuscular blockers does not incur a cost penalty.[1135] In this scenario, the use of intermediate-acting relaxants may decrease the time to extubation of the trachea and the incidence of residual neuromuscular block. They do not, however, shorten the length of ICU stay after bypass surgery.[1136] In the case of relaxant use for shorter surgical procedures, succinylcholine and mivacurium were found to be economically superior to all the other neuromuscular blockers for use during short operations when intense neuromuscular blockade was mandatory.[1137] However, once doses of neuromuscular blockers beyond the initial intubating dose are required, the cost of the use of mivacurium increases, and it becomes more expensive than intermediate-acting neuromuscular blockers.[1138]

The debate regarding cost and neuromuscular blocker use is ongoing. On one side, there is evidence that drug acquisition costs for nondepolarizing neuromuscular blockers can be decreased through physician education. On the other side is evidence suggesting that patients are placed at greater risk for complications associated with residual paralysis when long-acting nondepolarizing neuromuscular blockers are used. As described by Miller,[1139] any savings accrued by using long-acting as opposed to the shorter-acting neuromuscular blockers will be lost with the occurrence of a single adverse event as a result of residual neuromuscular blockade. For example, succinylcholine's side effects render it expensive to use despite its short duration of action. The true cost per dose of succinylcholine from society's perspective is not negligible and is more than 20 times the acquisition cost.[1140] Clinicians must constantly assess which neuromuscular blocking drug is best suited for their patients. The decision will be multifaceted and will have to include, in addition to the cost of the neuromuscular blocker, the duration and nature of the surgical procedure, as well as the patient's general health.

KEY POINTS

1. Two different populations of nicotinic acetylcholine receptors are found at the mammalian neuromuscular junction. In the adult, the nicotinic acetylcholine receptor at the postsynaptic (muscular) membrane is composed of $\alpha_2\beta\delta$ϵ-subunits. Each of the two α-subunits has an acetylcholine-binding site. The presynaptic (neuronal) nicotinic receptor is also a pentameric complex composed of $\alpha_3\beta_2$-subunits.
2. Nondepolarizing muscle relaxants produce neuromuscular blockade by competing with acetylcholine for the postsynaptic α-subunits. In contrast, succinylcholine produces prolonged depolarization that results in a decrease in sensitivity of the postsynaptic nicotinic acetylcholine receptor and inactivation of sodium channels so that propagation of the action potential across the muscle membrane is inhibited.
3. Different forms of neuromuscular stimulation test for neuromuscular blockade at

different areas of the motor end plate. Depression of the response to single-twitch stimulation is probably due to blockade of postsynaptic nicotinic acetylcholine receptors, whereas fade in the response to tetanic and train-of-four stimuli results from blockade of presynaptic nicotinic receptors.

4. Succinylcholine is the only available depolarizing neuromuscular blocker. It has a rapid onset of effect and an ultrashort duration of action because of its rapid hydrolysis by butyrylcholinesterase.

5. The available nondepolarizing neuromuscular blockers can be classified according to chemical class (steroidal, benzylisoquinolinium, or other compounds) or according to onset or duration of action (long-, intermediate-, and short-acting drugs) of equipotent doses.

6. The speed of onset is inversely proportional to the potency of nondepolarizing neuromuscular blocking drugs. With the exception of atracurium, molar potency is highly predictive of a drug's rate of onset of effect. Rocuronium has a molar potency ($ED_{95} \approx 0.54$ μM/kg) that is about 13% that of vecuronium and 9% that of cisatracurium. Its onset of effect is more rapid than that of either of these agents.

7. Neuromuscular blockade develops faster, lasts a shorter time, and recovers more quickly in the more centrally located neuromuscular units (laryngeal adductors, diaphragm, and masseter muscle) than in the more peripherally located adductor pollicis.

8. The long-acting neuromuscular blockers undergo minimal or no metabolism, and they are primarily eliminated, largely unchanged, by renal excretion. Neuromuscular blockers of intermediate duration of action have a more rapid clearance than the long-acting agents do because of multiple pathways of degradation, metabolism, and/or elimination. Mivacurium (a short-acting neuromuscular blocker) is cleared rapidly and almost exclusively by means of metabolism by butyrylcholinesterase.

9. After the administration of nondepolarizing neuromuscular blocking drugs, it is essential to ensure adequate return of normal neuromuscular function. Residual paralysis decreases upper esophageal tone, coordination of the esophageal musculature during swallowing, and the hypoxic ventilatory drive.

10. Defects in ion channels (channelopathies) in the presynaptic (neuronal) or postsynaptic (muscular) membrane of the neuromuscular junction result in a wide spectrum of muscle diseases.

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