Chapter 11

NEUROMUSCULAR BLOCKING AGENTS

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INTRODUCTION

The primary reason for administering neuromuscular blocking agents to casualties with traumatic injuries is to permit the airway to be secured with endotracheal intubation and mechanical ventilation. Because battlefield injuries can cause inadequate ventilation and oxygenation, intubation is often required. Many casualties with traumatic injuries have an altered level of consciousness and are at risk for aspiration of stomach contents because they are unable to protect the airway. On occasion, the casualty may simply be so confused and uncooperative that intubation with sedation and muscle relaxation may be required to care for him.

The first description of the clinical use of neuromuscular blockade was reported in 1932, when *d*-Tubocurarine was administered to control the muscle spasms of tetanus.[1] Since then, the pharmacology and clinical use of neuromuscular blocking agents, commonly referred to as muscle relaxants, have been greatly expanded. Today, these drugs are frequently used in surgery, the intensive care unit, and the emergency department. This chapter discusses the mechanisms of action, pharmacodynamics, uses, and complications of the most common neuromuscular blocking agents.

Classically, neuromuscular transmission is viewed as the release of the neurotransmitter substance *acetylcholine* at the motor nerve terminal in response to the neural action potential (Figure 11-1). A cationic channel protein on the postjunctional membrane possesses nicotinic cholinergic receptor sites. When these sites are occupied by acetylcholine or a suitable agonist, the receptor channel protein undergoes conformational change. This causes an influx of sodium ions and a corresponding efflux (although of lesser magnitude) of potassium ions. A smaller number of calcium ions then pass inward with the sodium, with a change in the endplate potential. Simultaneous opening of approximately 200,000 nicotinic receptor channels in response to the evoked release of acetylcholine generates a motor endplate potential. If this change in potential is of sufficient magnitude, the voltage-gated sodium ion channels of the adjacent muscle membrane open, and a large number of sodium ions pass into the interior of the cell, which depolarizes the cell. In some manner, this process is coupled to the activation of the contractile mechanism.[2] In addition to this mechanism, another population of cholinergic receptors appears to exist on the motor nerve terminal itself. Their physiological role is obscure, but their inactivation reduces the amount of acetylcholine that is released in response to a nerve impulse.

Through a combination of acetylcholine reuptake and local degradation within the synaptic cleft by the enzyme acetylcholinesterase, muscle repolarization occurs and the opportunity for contraction is restored. A second nonspecific plasma enzyme, pseudocholinesterase (ie, plasma cholinesterase), is also involved in the breakdown of acetylcholine and acetylcholine-like molecules.

It is customary to consider neuromuscular blocking agents in two groups: the *depolarizing* and the *nondepolarizing* agents. Depolarizing agents, of which succinylcholine is by far the best known, resemble acetylcholine stereochemically and mimic its action at the neuromuscular junction, causing depolarization of the endplate and adjacent muscle membrane, with clinically evident muscle fasciculations. The neuromuscular junction remains depolarized until succinylcholine diffuses away from the receptor site. Breakdown of succinylcholine occurs in a two-stage process away from the receptor site:

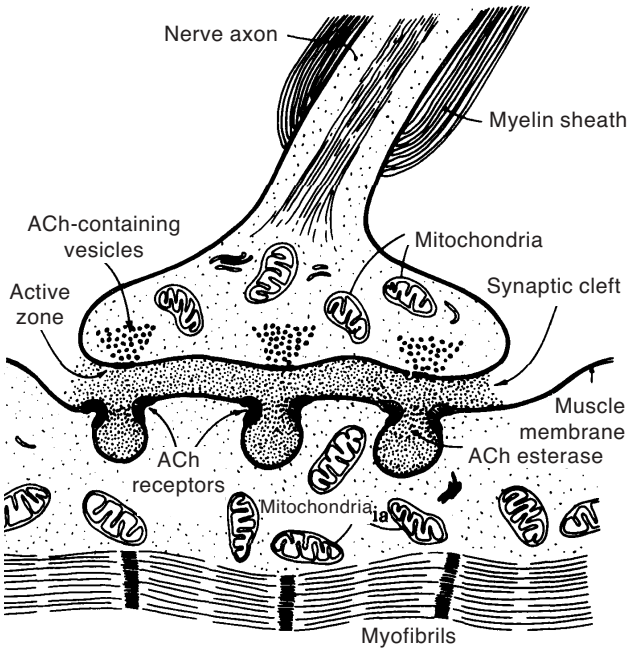

Fig. 11-1. The neuromuscular junction. Reprinted with permission from Shorten G. Neuromuscular blockade. In: Davison JK, Eckhardt WF III, Perese DA, eds. *Clinical Anesthesia Procedures of the Massachusetts General Hospital.* 4th ed. Boston, Mass: Little, Brown; 1993: 152.

1. pseudocholinesterase hydrolyzes succinylcholine to choline and succinylmonocholine (which has weak depolarizing relaxant activity), and
2. succinylmonocholine slowly breaks down to choline and succinic acid by the actions of both acetylcholinesterase and pseudocholinesterase.

Low pseudocholinesterase levels, drug-induced inhibition of cholinesterase activity, or the possession of a genetically atypical enzyme may be associated with prolonged neuromuscular blockade following the use of succinylcholine.

Nondepolarizing agents, on the other hand, act by passively binding acetylcholine receptor sites and thereby prevent their occupancy by acetylcholine. Because nondepolarizing agents act by blocking at the neuromuscular junction, muscle endplate depolarization and clinical fasciculations are not seen. The nondepolarizing agents are quaternary ammonium compounds that include two major categories: the steroid-based derivatives and the benzylisoquinoline series. Recovery from neuromuscular junction blockade occurs spontaneously but can be accelerated by the use of pharmacological agents that inhibit acetylcholinesterase, which therefore increases the availability of acetylcholine to compete for the binding site. Theoretically, experimental research drugs such as 4-aminopyridine can presynaptically increase the amount of acetylcholine and thereby competitively reverse the blockade caused by nondepolarizing agents. Currently, however, only the anticholinesterase agents are used clinically to antagonize neuromuscular junction blockade.

NEUROMUSCULAR MONITORING TECHNIQUES

It is important to emphasize that monitoring of neuromuscular function should be employed whenever neuromuscular blocking agents are used. The military anesthesiologist should consider four main questions when using neuromuscular blocking agents:

1. Is the blockade adequate?
2. Is the blockade excessive?
3. Can the blockade be reversed?
4. Is the blockade fully reversed?

Although there are many ways to stimulate a peripheral nerve, a typical commercially available hand-held peripheral nerve stimulator should provide the ability to choose stimulation by the single twitch, train-of-four (TOF), tetanic, and double-burst methods (Figure 11-2). The most commonly recommended method to monitor neuromuscular function is to observe the contraction of the fingers (adductor pollicis and flexor digitorum muscles) in response to electrical stimulation of the ulnar nerve at the wrist or elbow (Figure 11-3). Other areas may be stimulated, such as the facial nerve or the peroneal or posterior tibial nerves of the lower extremity (Figures 11-4 and 11-5). The magnitude of the muscle contraction response can be a rough gauge to monitor neuromuscular blockade. It is important to emphasize that direct muscle stimulation should be avoided, as this can be mistaken for the responses seen with nerve stimulation.

Fig. 11-2. The MiniStim is a portable, battery-operated, adjustable-amplitude, hand-held peripheral nerve stimulator. Photograph: Courtesy of Life-Tech, Inc, Houston, Tex.

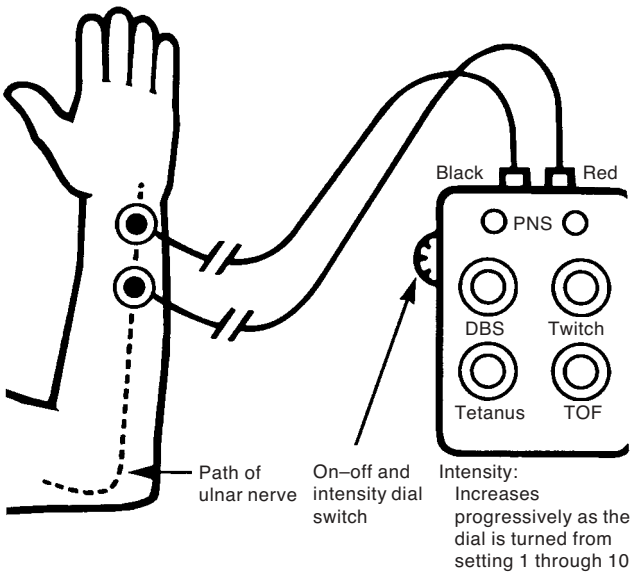

Fig. 11-3. Placement of nerve-stimulator electrodes over the ulnar nerve. Photograph: Courtesy of Organon, Inc, West Orange, NJ.

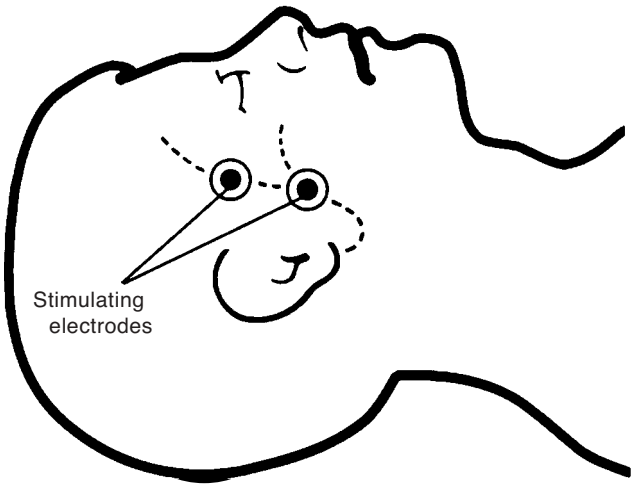

Fig. 11-4. Placement of nerve-stimulator electrodes over the facial nerve. Photograph: Courtesy of Organon, Inc, West Orange, NJ.

Single Twitch

A single supramaximal stimulus lasting less than 0.2 ms at a frequency of 0.1 Hz is employed to determine control muscle-contraction response before the neuromuscular blocking agent is administered. Subsequent single-twitch stimuli are then

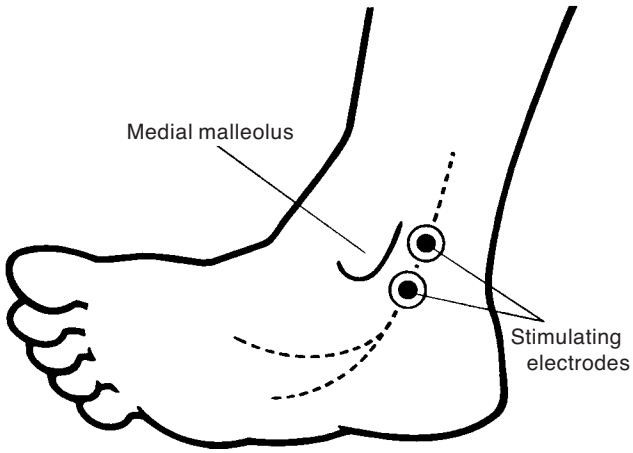

Fig. 11-5. Placement of nerve-stimulator electrodes over the posterior tibial nerve. Photograph: Courtesy of Organon, Inc, West Orange, NJ.

employed to assess the diminution of the twitch response so that the depth of muscle blockade can be gauged. This type of monitoring is only a crude measure unless a sophisticated recording device (eg, a force transducer) can be attached to the patient. Quantifying the loss of twitch height is crucial to assess the blockade accurately. For example, a 90% suppression of the twitch height is adequate for endotracheal intubation. Furthermore, 75% to 90% suppression is adequate for surgical relaxation in the presence of anesthetic agents, while a 25% suppression is only clinically associated with a decreased vital capacity. Unfortunately, 75% of receptors must be occupied with the neuromuscular blocking before there is a loss of twitch height. Given its minimal sensitivity, the single-twitch testing method is not recommended.

Train-of-Four

Four supramaximal stimuli at a frequency of 2 Hz are repeated at intervals longer than 10 seconds apart. The number of muscle-twitch responses corresponds to the degree of suppression of the initial twitch response. Loss of the fourth twitch (ie, only three twitches are seen) corresponds to a 75% suppression of the twitch height, compared to the control. Loss of the third, second, and first twitch responses corresponds to 80%, 90%, and 100% of the twitch height, respectively (Table 11-1). Monitoring the TOF is a very useful method of determining neuromuscular blockade because it does not re-

TABLE 11-1

CLINICAL EVALUATION OF NEUROMUSCULAR BLOCKADE

Train-of-Four Response (Twitches)	% Block (Approximate)	Clinical Implication of Neuromuscular Blockade
0	> 95	Response indicates clinical overdose of neuromuscular blockade
1	90	Blockade is adequate for intubation
2	80–90	Blockade is adequate for surgery or long-term ventilation
3	75–80	Additional dosing may be required for surgery or long-term ventilation
3–4	75	Patient is susceptible to reversal of neuromuscular blockade with anticholinesterase agents
4	≤ 75	Patient is recovering from neuromuscular blockade

quire a control height. Loss of more than three twitches signifies good intubating conditions, and maintenance of one to two twitches during continuous neuromuscular blockade confirms adequate relaxation and preserves the ability to reverse the neuromuscular blocking agents. Total loss of the four twitches during incremental-bolus or continuous-infusion therapy signifies excessive blockade. A return of the TOF twitch response suggests recovery from neuromuscular blockade (Figure 11-6).

Tetanic Stimulation

Tetanic nerve stimulation varies in frequency from 50 to 200 Hz, with 50 Hz or 100 Hz being more commonly employed. Tetanic stimulation at 50 Hz for 5 seconds is clinically useful to estimate peak muscle tension. Stimulation at this frequency corresponds to what may be seen with maximum voluntary muscular effort. Peak muscle tension in response to tetanic stimulation is reduced in the presence of both depolarizing and nondepolarizing blockade, but fade to tetanic stimulation is only seen with the latter. This fade to tetanus is a preneuromuscular junction phenomenon. It is due to curare-like drugs acting on acetylcholine mobilization during high-frequency stimulation. Evidence of fade with tetanus suggests incomplete recovery from the neuromuscular blocking agents (Figure 11-7). Fade is termed *recurarization* if it is seen after clinical recovery has been determined. Tetanic stimulation is painful and should only be employed with this consideration in mind.

Double-Burst Stimulation

Double-burst stimulation is two, short, 50-Hz tetanic stimuli delivered 750 ms apart. If the response to the second stimulation is less than the first, then residual curarization can be suspected. This method is more sensitive in detecting residual curarization than other methods. As with tetanic stimulation, double-burst stimulation is also painful to apply.

Clinical Assessment

Although the use of a nerve stimulator is strongly recommended when neuromuscular blocking agents are being employed, this type of monitor may be unavailable to the anesthesiologist in the field setting. The clinician must then gauge the degree of muscle strength that has returned so that the casualty's readiness for extubation can be assessed. The casualty's ability to sustain a head lift for 5 seconds, demonstrate a vital capacity of 15 to 20 mL/kg, or generate an inspiratory force of –25 cm H_2O pressure corresponds clinically to a TOF ratio greater than 0.75 or sustained tetanus at 50 Hz for 5 seconds. The ability to cough effectively may also indicate adequate respiratory muscle strength for extubation. Finally, the demonstration of a normal expiratory flow rate, vital capacity, and inspiratory force greater than 40 cm H_2O pressure can be equated with a TOF ratio of 1.0, indicating full recovery from neuromuscular blockade.

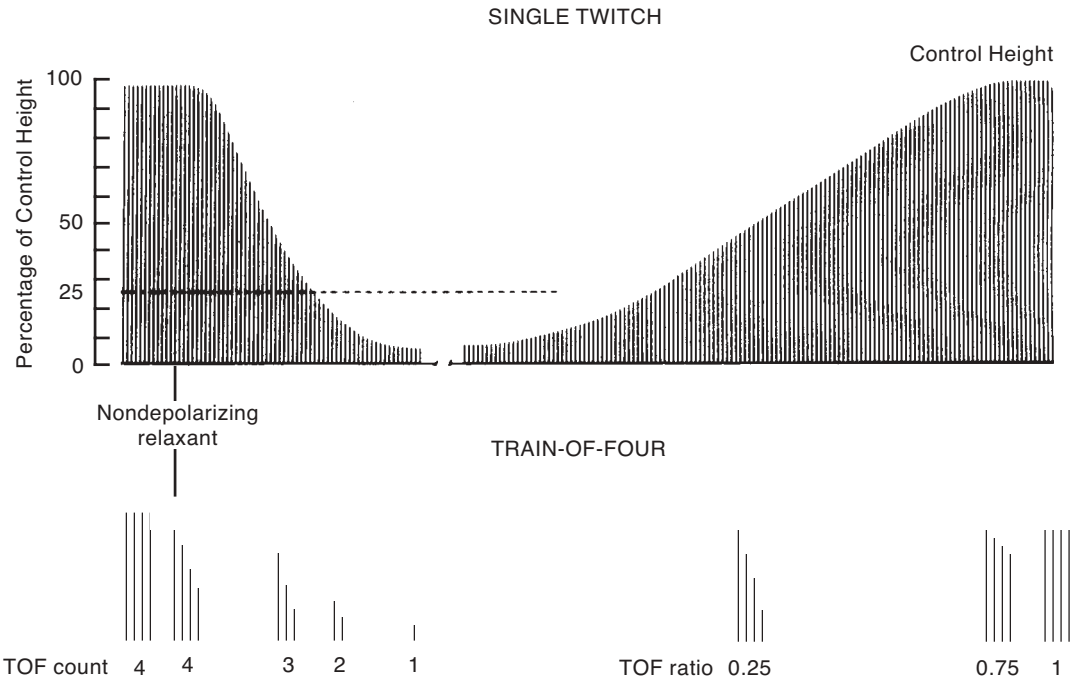

Fig. 11-6. Graphic demonstrations of single-twitch (above) and train-of-four response (below) during onset of and recovery from nondepolarizing neuromuscular blockade. Reprinted with permission from Shorten G. Neuromuscular blockade. In: Davison JK, Eckhardt WF III, Perese DA, eds. *Clinical Anesthesia Procedures of the Massachusetts General Hospital*. 4th ed. Boston: Mass: Little, Brown; 1993: 167.

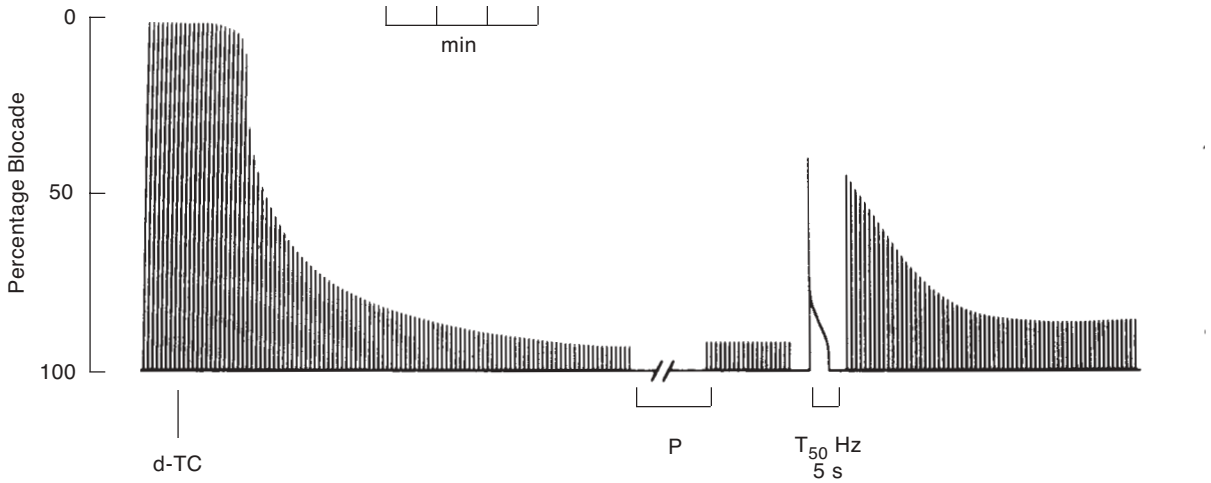

Fig. 11-7. Loss of response to 0.1 Hz after *d*-Tubocurarine (left). Decrease in peak muscle tension followed by fade (no sustained response) after 50-Hz tetanic stimulation (right). Reprinted with permission from Shorten G. Neuromuscular blockade. In: Davison JK, Eckhardt WF III, Perese DA, eds. *Clinical Anesthesia Procedures of the Massachusetts General Hospital*. 4th ed. Boston, Mass: Little, Brown; 1993: 158.

INDICATIONS FOR NEUROMUSCULAR BLOCKADE

Neuromuscular blocking agents are routinely used as adjuncts for general anesthesia. Their most common use is in the facilitation of endotracheal intubation. For elective surgery, general anesthesia is typically induced with a hypnotic agent such as thiopental sodium and a narcotic. Once the patient is asleep and the ability to ventilate the patient with a bag-valve-mask system is confirmed, a muscle relaxant is administered to relax the jaw, larynx, and diaphragm, and thus to facilitate smooth endotracheal intubation. Without a neuromuscular blocking agent, a deeper plane of anesthesia is required to achieve the best possible intubating conditions, which may cause significant hypotension and other detrimental side effects in some patients.

During the maintenance of general anesthesia, supplemental doses of neuromuscular blocking agents are often given to provide optimal operating conditions for the surgeon. This is especially important in abdominal surgery because the anesthetic agents alone do not provide adequate muscle relaxation for these procedures unless very high doses are used.

There is currently great controversy surrounding the use of muscle relaxant agents outside the operating room, particularly in the intensive care unit. Muscle relaxation to facilitate endotracheal intubation by eliminating biting, gagging, combativeness, and laryngospasm is probably the most common clinical indication for their use outside the operating room. Caution in using neuromuscular blocking agents for this purpose must be exercised, particularly in those patients who may be identified as difficult to intubate. The need for a possible surgical airway should be understood, and trained personnel should be available. Physicians who prescribe neuromuscular blockade should be trained experts in airway-management techniques. It is important to realize that once muscle relaxants are given, the patient will be totally dependent on controlled ventilation until the drug is eliminated or antagonized. If the airway cannot be controlled, the patient will asphyxiate.

Many clinicians contend that there is no role for these drugs in appropriately sedated patients in the intensive care unit.[3] It is important to stress that muscle relaxation should never be used without concomitantly administering sedation in doses adequate to produce amnesia or unconsciousness. Furthermore, the use of neuromuscular blocking agents should be limited to the shortest possible time. Generally accepted clinical applications include those listed in Exhibit 11-1.

Rarely, neuromuscular blockade can aid in the treatment of medical conditions such as tetanus, where muscular contraction is itself harmful.[4] Likewise, patients suffering from cardiovascular or metabolic instability due to intractable convulsive activity may transiently benefit from neuromuscular blockade. Because muscle relaxant agents do nothing to protect the brain or terminate intracerebral seizure activity, continuous electroencephalographic monitoring is recommended when the clinical signs of seizure activity are abolished by their use.[5]

The use of a muscle relaxant may occasionally be a useful adjunct to sedative agents when obtaining diagnostic procedures or studies.[6] There are rare patients (eg, those with alcohol withdrawal) whose combativeness may endanger themselves despite large amounts of sedative agents. In situations of this type, muscle relaxants may be necessary temporarily to avoid injury. In addition, these agents have been used to prevent muscle-activity–induced increases in intracranial pressure in patients with head injury.

Neuromuscular blocking agents are useful in facilitating mechanical ventilation in the intensive care unit.[7,8] Certain modes of mechanical ventila-

EXHIBIT 11-1

RATIONALES FOR NEUROMUSCULAR BLOCKADE IN THE INTENSIVE CARE UNIT

- Facilitate endotracheal intubation
- Minimize increased oxygen consumption associated with muscular activity
- Abolish ventilator–patient discoordination
- Establish pharmacological restraint
- Adjunct to treat septic shock complicated by acute respiratory failure
- Rest fatigued respiratory musculature

Adapted with permission from Hall JB, Schmidt GA, Wood LDH. *Principles of Critical Care*. New York, NY: McGraw Hill; 1992: 976.

tion that use prolonged inspiratory times may be actively opposed by the patient. Allowing permissive hypercapnia and using high levels of positive end-expiratory pressure may be uncomfortable to the patient, thus requiring muscle relaxation. Although the use of sedation alone is usually sufficient, some patients demonstrate a respiratory pattern that is discordant with settings chosen for the mechanical ventilator. The resulting bucking and straining against the ventilator may provoke pulmonary barotrauma and bronchospasm. Most often, this discordancy signals that ventilator settings are not suited to the patient's requirements. Adjustment of the ventilator settings must be considered prior to the institution of muscle-relaxant therapy.

Theoretically, muscle relaxation can be used to reduce oxygen consumption in patients with marginal oxygenation. Oxygen consumption by ventilatory muscles is normally 1% to 3% of the available supply. In acute respiratory distress, the oxygen cost of breathing can increase to 24% of the supply.[9] This increased oxygen consumption and perfusion of the stressed respiratory muscles that accompanies the adult respiratory distress syndrome may potentially deprive the body of desperately needed energy supplies when oxygen transport is impaired by a reduction in cardiac output, hypoxemia, or anemia.[10] Neuromuscular blockade has been shown to improve arterial oxygenation and decrease oxygen consumption in patients suffering from respiratory failure, although it has not yet been shown to improve patient outcome.[7,11]

TYPES OF MUSCLE RELAXANTS

Muscle relaxants are classified as depolarizing or nondepolarizing. The only depolarizing agent in clinical use in the United States is succinylcholine chloride. All other muscle relaxants in clinical use are nondepolarizing in their mechanism of action.

Succinylcholine Chloride

Succinylcholine, consisting of two linked acetylcholine molecules, is a potent acetylcholine agonist with a rapid onset of action (< 1 min) and brief duration at clinically used doses (5–10 min). Because of these characteristics, it is an ideal agent in situations where expedient endotracheal intubation is required. The intravenous dose used for intubation is 1 to 1.5 mg/kg in adults and 2 to 2.5 mg/kg in children younger than 2 years of age.[12] In emergency situations where intravenous access is unavailable, succinylcholine can be administered intramuscularly in a dose of 4 mg/kg, with a rapid onset of activity. Great caution should be exercised when using succinylcholine in children, especially boys under the age of 8 years. There have been isolated reports of a succinylcholine-induced hyperkalemic cardiac arrest in this cohort that may be related to an undiagnosed muscular dystrophy, typically of the Duchenne type.

Succinylcholine is rapidly degraded by pseudocholinesterase. Its duration of action may be increased owing to deficiencies in the amount of enzyme (eg, as is seen in patients with liver disease, pregnancy, cytotoxic agents, and malnutrition).[13,14] In addition, genetic abnormalities exist: abnormal isozymes are estimated to occur in 1 per 3,000 in the general population.[15] Even in situations such as these, the duration of muscle relaxation is rarely longer than 20 to 30 minutes.[13–15] If it is necessary to antagonize the prolonged neuromuscular blockade caused by succinylcholine, then administering fresh frozen plasma to provide pseudocholinesterase is effective.[16]

The administration of succinylcholine has been associated with many adverse effects. The serum potassium level is expected to rise from 0.5 to 1.0 mEq/L because potassium leaks from the muscle cell during depolarization. High serum-potassium concentrations have been specifically reported after administration of succinylcholine in patients with spinal cord transection, nerve damage, burns, major central nervous system injuries, and prolonged periods of immobility.[17,18] The common factor that appears to link these conditions and the potential for succinylcholine-induced hyperkalemia is a proliferation of nicotinic cholenergic receptors on myocytes located a*way* from the neuromuscular junctions. Such nonjunctional, or extrajunctional, receptors, when stimulated, remain open 4-fold longer than normal junctional receptors, a difference that greatly increases the time for potassium flux.[19] It is therefore unwise to administer succinylcholine to such patients after the first 24 hours from injury, although this effect can be delayed up to 1 week from injury. Succinylcholine may safely be administered during the first hours after a traumatic injury. The risk of ventricular fibrillation or cardiac arrest due to hyperkalemia may persist for 6 months or longer after initial injury in these patients.[20] Life-threatening hyperkalemic events can be treated in the usual fashion with insulin, calcium, and sodium bicarbonate.

Succinylcholine can cause an increase in intraocular pressure and should therefore be used cautiously in patients who have penetrating injuries of the globe and some types of glaucoma. Controversy exists as to whether succinylcholine should be used in patients who may have increased intracranial pressure. After succinylcholine has been administered, small increases in intracranial pressure have been detected in patients whose pressure previously was normal.[21] On the other hand, the advantage of using succinylcholine in patients who require tracheal intubation is that it produces a rapid and profound neuromuscular blockade, which attenuates any substantial increase in intracranial pressure due to coughing or bucking during the intubation process.

Another potential adverse effect of succinylcholine is the rare malignant hyperthermia syndrome. This hypermetabolic syndrome manifests with severe metabolic acidosis and carries a high mortality if not aggressively treated. The key to treatment is early administration of dantrolene sodium and supportive therapy until the acidosis and its sequelae resolve. (For a more complete discussion, see Chapter 29, Malignant Hyperthermia: Military Implications.)

Repeated bolus dosing of succinylcholine should be avoided: it may cause profound bradycardia due to repeated stimulation of the muscarinic receptors. Although this drug is available as a continuous infusion, its use by this method is not recommended. Long-term administration of succinylcholine with doses higher than 5 mg/kg alters the character of the blockade to that of a nondepolarizing muscular blockade. This is termed a Phase II blockade and has the clinical and electromyographic characteristics of a nondepolarizing neuromuscular blockade.

Given its many side effects, the clinical trend has been to avoid the routine use of succinylcholine for intubation and general anesthesia in elective surgery. However, when rapid control of the airway is required, succinylcholine remains the drug of choice for most clinicians.

Nondepolarizing Agents

Nondepolarizing agents act as competitive inhibitors at the motor endplate, preventing acetylcholine from binding at receptor sites and therefore interrupting neuromuscular transmission. Neuromuscular blockade is the result. Because of their competitive mechanisms of action, the effects of these drugs can be antagonized (ie, reversed) with acetylcholinesterase inhibitors such as neostigmine, pyridostigmine, or edrophonium. The reversal agent will also increase acetylcholine at both the nicotinic and muscarinic cholinergic receptors, with resultant bradycardia and other unpleasant muscarinic effects. Therefore, anticholinergic drugs such as atropine or glycopyrrolate should accompany the use of acetylcholinesterase inhibitors when antagonizing neuromuscular blockade. The nondepolarizing neuromuscular blocking agents and their characteristics are found in Table 11-2.[22] The recommended dosages for the acetylcholinesterase inhibitor drugs and the antimuscarinic agents used for reversal of nondepolarizing neuromuscular blockade are found in Table 11-3.

Pancuronium Bromide

Pancuronium is an aminosteroid neuromuscular blocking agent with a long-acting duration of action. Following a dose of 0.08 to 0.12 mg/kg, administered intravenously, pancuronium will produce adequate relaxation for intubation in 90 to 120 seconds, with a duration of approximately 60 minutes.[23] Pancuronium undergoes substantial hepatic metabolism; however, its metabolites are partially active and depend on renal excretion.[8] Owing to these metabolites, this drug is a poor choice for patients with renal failure, and hemodialysis is ineffective for its elimination.[24] Increases in the half-life of pancuronium also occur with liver failure. Thus, any patient with compromised hepatic or renal function is at risk for prolonged neuromuscular blockade during pancuronium administration. Pancuronium also demonstrates vagolytic effects that cause tachycardia.[25] Generally, the use of pancuronium in all settings has decreased in the last several years as newer nondepolarizing drugs with fewer side effects, faster onset, and shorter duration have become available.

Vecuronium Bromide

Vecuronium is the 2-desmethyl analog of pancuronium. It has an intermediate duration of action, with an onset of dense neuromuscular blockade in 2 to 3 minutes following a dose of 0.1 mg/kg. The drug is in large part removed via hepatic metabolism and biliary excretion, and is therefore a poor choice for patients with liver disease.[26] Vecuronium has an active 3-desacetyl metabolite. Renal clearance accounts for up to 25% of the parent compound and its metabolite's excretion. Drug accumulation may account for prolonged recovery in patients with renal failure. Vecuronium has no autonomic or vagal blocking activities, and its use

TABLE 11-2

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Drug	Intubating Dose (mg/kg)	25% Recovery of Control Height (min)	Infusion Rate (μg/kg/min)
Pancuronium bromide (LA)	0.08–0.12	60–120	0.3–0.8
Vecuronium bromide (IA)	0.1–0.2	45–90	0.8–2.0
Atracurium besylate (IA)	0.5–0.6	30–45	4–12
Mivacurium chloride (SA)	0.2–0.25	15–20	3–15
Rocuronium bromide (SO-IA)	0.6–1.0	45–75	8–12
Pipecuronium bromide (LA)	0.8–0.12	60–120	NA
Doxacurium chloride (LA)	0.05–0.08	90–150	NA
51W89 (atracurium stereoisomer)* (Mfg: Burroughs Wellcome, Research Triangle Park, NJ)	0.15–0.2	40–75	1–2
ORG 9487 (steroid based)* (Mfg: Organon, West Orange, NJ)	1.5	24	NA

*Investigational drug
LA: long acting; IA: intermediate acting; SA: short acting; SO-IA: short onset and intermediate acting; NA: information not available

offers hemodynamic stability.[27] In addition, the absence of histamine release during its administration makes it attractive for use in patients with reactive airway disease. Its shorter duration of action makes this drug more titratable than pancuronium. Vecuronium has one advantage of considerable military medical importance, which it shares only with succinylcholine: it is available as a lyophilized powder and can be stored without refrigeration.

Atracurium Besylate

Atracurium is an intermediate-acting neuromuscular blocking agent with onset characteristics approximately equal to vecuronium at an equivalent

TABLE 11-3

NEUROMUSCULAR BLOCKADE REVERSAL AGENTS

Neuromuscular Blocking Agent	Dose (mg/kg)	Time to Peak Antagonism (min)	Duration of Antagonism (min)	Antimuscarinic Agent	Dose (μg/kg)
Edrophonium	0.5–1.0	1	40–65	Atropine	7–10
Neostigmine	0.03–0.06	7	55–75	Atropine	15–30
				Glycopyrrolate	10–15
Pyridostigmine	0.25	10–13	80–130	Atropine	15–20
				Glycopyrrolate	10–15

Adapted with permission from Shorten G. Neuromuscular blockade. In: Davison JK, Eckhardt WF III, Perese DA, eds. *Clinical Anesthesia Procedures of the Massachusetts General Hospital*. 4th ed. Boston, Mass: Little, Brown; 1993: 163.

dosage that produces skeletal muscle relaxation in 95% of subjects (ED_{95}). Atracurium has potential advantages in patients who have hepatic or renal failure, because it undergoes extensive plasma degradation.[28] Additionally, atracurium is metabolized via the Hofmann elimination pathway. Hofmann elimination[29] is the spontaneous degradation of atracurium at physiological pH and temperature into laudanosine and a monoquaternary acrylate. Since Hofmann degradation does not require complete organ function or enzymes for its metabolism, there is no significant prolongation of its action in patients with renal or hepatic dysfunction.[30,31] Although the clinical importance of laudanosine in humans is uncertain, this metabolite causes seizures when high doses are given to animals.[32] However, this association with seizures has not been demonstrated in humans.

Atracurium has minimal cardiovascular effects following single- or incremental-dose administration sufficient to cause adequate relaxation for intubation and surgical procedures. In susceptible individuals, large-bolus doses of atracurium administered over a short time may induce bronchospasm or hypotension due to histamine release.

Mivacurium Chloride

Mivacurium chloride is the newest benzisoquinolinium nondepolarizing muscle relaxant. Its onset characteristics are similar to those of atracurium and vecuronium, but it has a shorter duration of action. Its short duration, like succinylcholine's, results from its rapid metabolism by pseudocholinesterases. At clinically used doses, mivacurium releases significant amounts of histamine, with a resultant potential for inducing hypotension and bronchospasm. Like patients who have received succinylcholine, those with deficient or atypical pseudocholinesterase may have greatly prolonged neuromuscular blockade. The primary use of mivacurium is in surgery of short duration, especially if there is a contraindication for the use of succinylcholine.

Rocuronium Bromide

Rocuronium is the latest muscle relaxant to be introduced into clinical practice in the United States. While structurally analogous to vecuronium and pancuronium, it has much faster onset characteristics.[33,34] Given in appropriate doses (3- to 4-fold > ED_{95}), its profile of clinical onset after administration is comparable to that of succinylcholine.[34] Like vecuronium, rocuronium depends primarily on the liver for metabolism and is excreted by the biliary system.[35,36] The duration of rocuronium is comparable to that of vecuronium (2- to 4-fold > ED_{95}).[34]

The onset characteristics of this drug are a major advance in muscle-relaxant pharmacology, allowing clinicians to perform reliable, rapid endotracheal intubations with excellent intubating conditions in 60 to 90 seconds without succinylcholine. Like other currently available nondepolarizing muscle relaxants, rocuronium's duration of effect is much longer than succinylcholine's, which may limit its use in some situations. However, given circumstances where a muscle relaxant is indicated for rapid intubation and succinylcholine is contraindicated, rocuronium is the best alternative currently available.

Because all patients requiring emergency intubation are considered to be at risk for aspiration of stomach contents during the intubation sequence, a rapid-sequence intubation with cricoid pressure is commonly performed. If muscle relaxants are to be used to facilitate intubation, a fast-acting agent should be selected so that the trachea can be intubated promptly and the airway protected. Succinylcholine is most commonly used in this scenario. The list of contraindications and risks with the use of succinylcholine should be considered. Most patients with acute (< 24 h) trauma can safely be given succinylcholine, and the risks of using this agent should not be overstated. The most reasonable alternative is rocuronium, which has a similarly fast onset at a dose of 0.9 to 1.2 mg/kg (3- to 4-fold > ED_{95}) but much longer duration (50–90 min). Rocuronium should be substituted in the patient with a normal airway who has trauma (including burns) greater than 24 hours old, increased intracranial pressure, history of neurologic disease, significantly increased serum potassium (renal failure), penetrating eye injury, or a family history of malignant hyperthermia. The primary disadvantage of rocuronium at this dosage is the duration of neuromuscular blockade: 1 hour or longer.

Other Agents

Newer neuromuscular blocking agents currently available for use in the operating room or the intensive care unit include the long-acting drugs benzylisoquinoline doxacurium chloride and aminosteroid pipecuronium bromide. Many other investigational agents are currently being studied. These newer agents have minimal cardiovascular effects, but their usefulness in the clinical setting remains to be determined.

COMPLICATIONS OF NEUROMUSCULAR BLOCKADE

As with all interventions, the use of neuromuscular blocking agents has associated risks and complications. It is important to realize that when a muscle relaxant is administered, the patient will be unable to ventilate on his own. Therefore, some method of ventilation must be supplied externally. Neuromuscular blocking agents should never be administered unless the necessary equipment is available to supply this need. In a patient who is not already intubated or who does not have a tracheostomy, at a minimum there should be a laryngoscope with different types of blades, endotracheal tubes, suction, an oxygen supply, and a method to deliver positive-pressure ventilation (eg, bag-valve-mask system, mechanical ventilator). The possibility of difficult intubation should be considered. This cannot be emphasized strongly enough: if the airway is not secured in some manner after the muscle relaxant is administered, the patient will suffocate.

Once intubated, the most serious risk to the patient is accidental disconnection from the mechanical ventilator. Another risk is that the patient will fail to cough during tracheal suction, which can lead to retention of secretions. In addition to these, an increased risk of pulmonary embolism has been described.[37] Patients under neuromuscular blockade are also prone to develop decubitus ulcers and nerve-compression syndromes. In addition, owing to these concerns, the nursing workload increases appreciably when patients are treated with neuromuscular blocking agents.

Recently, numerous reports[38–41] have implicated muscle relaxants as causing generalized weakness or myopathy following their long-term administration, with recovery periods lasting as long as 6 months. These reports have implicated the aminosteroid-based agents primarily, although a later report[42] suggests that any of the neuromuscular blocking agents may be involved. However, it is not yet clear whether muscle relaxants are the precipitating factor. Other possible contributing factors have been identified, including polyneuropathy and polymyopathy of critical illness, disuse atrophy, aminoglycoside use, and, in particular, steroid administration.[43–45] Particularly noteworthy are the numerous reports describing otherwise healthy patients suffering from asthma who were simultaneously treated with corticosteroids and muscle relaxants for acute respiratory failure.[46,47] Patients who have muscle weakness or difficulty in weaning from ventilatory management may need electromyographic or histological studies to delineate their basic neuromuscular problems. Drug interactions may affect the degree and duration of neuromuscular blockade. The aminoglycosides can prolong the action of nondepolarizing agents. The mechanisms of action include inhibition of presynaptic acetylcholine release and stabilization of postjunctional membranes.[48] Patients on anticonvulsants or aminophylline may be more resistant to depolarizing agents.[49]

The soldier on the battlefield where unconventional weapons have been or might be used may present for anesthesia and surgery after having been exposed to a variety of agents that impact on the management of neuromuscular blocking agents and anesthesia. These agents include not only chemical warfare agents but also pyridostigmine, which would have been given to the soldiers for nerve agent prophylaxis, and atropine and cholinesterase reactivators such as 2-pyridine aldoxime methyl chloride (2-PAM Cl), with which soldiers are expected to treat themselves immediately after exposure. Medical officers who are performing triage on chemical casualties who also need surgery may not be able to ascertain exactly how much nerve agent, prophylactic agent, and early treatment drugs the casualty has received. This topic is discussed more fully in Chapter 30, Anesthesia for Casualties of Chemical Warfare Agents.

SUMMARY

Muscle relaxants have four important adjunctive roles in the management of combat casualties: (1) to assist in airway intubation; (2) to optimize operative exposure, especially during laparotomy; (3) to assure a quiet operating field; and (4) to assure adequate mechanical ventilation to patients in the intensive care ward. Muscle relaxants such as succinylcholine, which depolarizes motor endplates, have a rapid onset and a short duration of action. Unfortunately, the use of succinylcholine in certain types of casualties (eg, those with chronic burns or injuries to the spinal cord, or who are recovering from massive injury) has been associated with fatal cardiac dysrhythmias due to hyperkalemia. Succinylcholine should not be used in such casualties, nor in casualties in whom the initial increase in local muscle tension caused by depolarization is undesirable. An example of the latter contraindication is the casu-

alty with a penetrating wound of the eye, in whom prolapse of the intraocular contents is possible.

Nondepolarizing muscle relaxants block the acetylcholine receptor without causing depolarization. They typically have a slower onset of action than does succinylcholine, but their duration of action is more prolonged. Nondepolarizing neuromuscular blocking agents may be used when succinylcholine is contraindicated or when the casualty has impaired cardiovascular function. When quantitative assessments of neuromuscular function using a nerve stimulator cannot be made, extubation of a casualty who has received a muscle relaxant should be considered only after return of muscle function is assessed by the patient's ability to sustain a 5-second head lift and to generate an inspiratory force of –25 cm H_2O pressure. Some of the newer nondepolarizing muscle relaxants such as atracurium, vecuronium, and rocuronium are not dependent on renal metabolism and should be considered safe to administer to patients in acute renal failure.

The use of neuromuscular blocking agents in casualties who have been exposed to nerve agents, and in those who have been given nerve agent prophylaxis in the form of pyridostigmine, can cause special treatment problems for military anesthesia providers. Soldiers who have received pyridostigmine may be especially sensitive to succinylcholine, while simultaneously being relatively refractory to the effects of nondepolarizing agents.

REFERENCES

1. West R. Curare in man. *Proc R Soc Med*. 1932;25:1107–1116.
2. Torda TA. The neuromuscular blocking drugs. *Med J Aust*. 1988;149:316–319.
3. Wheeler AP. Sedation, analgesia and paralysis in the ICU. *Chest*. 1993;104:566–577.
4. Peat SJ, Potter DR, Hunter JM. The prolonged use of atracurium in a patient with tetanus. *Anaesthesia*. 1988;43:962–963.
5. Delgado-Escueta AV, Wasterlain C. Management of status epilepticus. *N Engl J Med*. 1982;306:1337–1340.
6. Roberts DJ, Clinton JE, Ruiz E. Neuromuscular blockade for critical patients in the emergency department. *Ann Emerg Med*. 1986;15:152–156.
7. Coggeshall JW, Marini JJ, Newman JH. Improved oxygenation after muscle relaxation in adult respiratory distress syndrome. *Arch Int Med*. 1985;145:1718–1720.
8. Buck ML, Reed MD. Use of nondepolarizing neuromuscular blocking agents in mechanically ventilated patients. *Clin Pharm*. 1991;10:32–48.
9. Hubmayr RD, Abel MD, Rehder K. Physiologic approach to mechanical ventilation. *Crit Care Med*. 1990;18:103–113.
10. Roussos C, Macklem PT. The respiratory muscle. *N Engl J Med*. 1982;307:786–797.
11. Bishop MJ. Hemodynamic and gas exchange effects of pancuronium bromide in sedated patients with respiratory failure. *Anesthesiology*. 1984;60:369–371.
12. Durbin CG Jr. Neuromuscular blocking agents and sedative drugs: Clinical uses and toxic effects in the critical care unit. *Crit Care Clin*. 1991;7:489–506.
13. Whittaker M. Plasma cholinesterase variants and the anaesthetist. *Anaesthesia*. 1980;35:174–197.
14. Evans RT, Wroe JM. Plasma cholinesterase changes during pregnancy: Their interpretations as a cause of suxamethonium-induced apnoea. *Anaesthesia*. 1980;35:651–654.
15. Viby-Mogensen J. Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with genotypically normal enzyme. *Anesthesiology*. 1980;53:517–520.

16. Epstein HM, Jarzemsky D, Zuckerman L, Vagher P. Plasma cholinesterase activity in the blood bank. *Anesth Analg*. 1980;59:211–214.

17. Isenstein DA, Venner DS, Duggan J. Neuromuscular blockade in the intensive care unit. *Chest*. 1992;102:1258–1266.

18. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. *Anesthesiology*. 1975;43:83–99.

19. Brenner HR, Samann B. Neurotrophic control of channel properties at neuromusclar synapses of rat muscle. *J Physiol* (Lond). 1983;337:159–166.

20. Sharpe MD. The use of muscle relaxants in the intensive care unit. *Can J Anesth*. 1992;39:949–962.

21. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. *Anesthesiology*. 1986;65:165–169.

22. Savarese JJ, Miller RD, Lien CA, Caldwell JE. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. *Anesthesia*. 4th ed. New York, NY: Churchill Livingstone; 1994: 417–487.

23. Hilgenberg JC. Comparison of the pharmacology of vecuronium and atracurium with that of other currently available muscle relaxants. *Anesth Analg*. 1983;62:524–531.

24. Sangala W, Dixon J. Pancuronium and renal failure. *Anaesthesia*. 1987;42:1236. Letter.

25. Kelman GR, Kennedy BR. Cardiovascular effects of pancuronium in man. *Br J Anaesth*. 1971;43:335–338.

26. Lebrault C, Berger JL, D'Hollander AA, Gomeni R, Henzel D, Duvaldestin P. Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. *Anesthesiology*. 1985; 62:601–605.

27. Robertson EN, Booij LH, Fragen RJ, Crul JF. Clinical comparison of atracurium and vecuronium (ORG NC 45). *Br J Anaesth*. 1983; 55:125–129.

28. Fisher DM, Canfell PC, Fahey MR, et al. Elimination of atracurium in humans: Contribution of Hofman elimination and ester hydrolysis versus organ based elimination. *Anesthesiology*. 1986;65:6–12.

29. Hofmann AW. Beitrages zur Kenntriss der fluchtragen organischen Basen. *Ann Chem.* 1851;78:253–259.

30. Nigrovic V, Fox JL. Atracurium decay and the formation of laudanosine in humans. *Anesthesiology*. 1991;74:446–454.

31. Fahey MR, Rupp SM, Fisher DM, et al. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology*. 1984; 61;699–702.

32. Chapple DJ, Miller AA, Ward JB, Wheatley PL. Cardiovascular and neurological effects of laudanosine: Studies in mice and rats, and in conscious and anesthetized dogs. *Brit J Anaesth*. 1987; 59:218–225.

33. Bowman WC, Rodger IW, Houston J, Marshall RJ, McIndewar I. Structure:action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat. *Anesthesiology*. 1988;69:57–62.

34. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology*. 1993; 79:913–918.

35. Khuenl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. *Anesthesiology*. 1990;72:669–674.

36. Magorian T, Wood P, Caldwell J, et al. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg*. 1995;80:754–759.

37. Miller-Jones CM, Williams JH. Sedation for ventilation: A retrospective study of fifty patients. *Anaesthesia*. 1980; 35:1104–1106.

38. Gooch JL, Suchyta MR, Balbierz JM, Pentajan JH, Clemmer TP. Prolonged paralysis after treatment with neuromuscular blocking agents. *Crit Care Med*. 1991;19:1125–1131.

39. Vanderheyden BA, Reynolds HN, Gerold KB, Emanuele T. Prolonged paralysis after long-term vecuronium infusion. *Crit Care Med*. 1992; 20:304–307.

40. Margolis B, Khachikeon M, Friedmen Y, Gorrad C. Prolonged reversible quadriparesis in mechanically ventilated patients who received long-term infusions of vecuronium. *Chest*. 1991; 100:877–878.

41. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long term administration of vecuronium. *N Engl J Med*. 1992;327:524–528.

42. Manthous CA, Chatila W. Prolonged weakness after the withdrawal of atracurium. *Am J Respir Crit Care Med*. 1994;150:1441–1443.

43. Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy: A complication of sepsis and multiple organ failure. *Brain*. 1987;110:819–841.

44. Danon MJ, Carpenter S. Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. *Muscle Nerve*. 991;14:1131–1139.

45. Vital Brazil O, Prado-Franceschi J. The nature of neuromuscular block produced by neomycin and gentamicin. *Arch Int Pharmacodyn Ther*. 1969;179;78–85.

46. Douglass JA, Tuxen DV, Horne M, et al. Myopathy in severe asthma. *Am Rev Respir Di*s. 1992;146:517–519.

47. Williams TJ, O'Hehir RE, Czarny D, Horne M, Bowes G. Acute myopathy in severe asthma treated with intracavernously administered corticosteroids. *Am Rev Respir Dis*. 1988;137:460–463.

48. Sokoll MD, Gergis SD. Antibiotics and neuromuscular function. *Anesthesiology*. 1981;55:148–159.

49. Doll DC, Rosenberg H. Antagonism of neuromuscular blockage by theophylline. *Anesth Analg*. 1979;58:139–140.