Chapter 15

Muscle Relaxants and Neuromuscular Blockade

Elizabeth A. Martinez and Robert D. Keegan

Introduction

Muscle relaxants are anesthetic adjuncts administered to improve relaxation of skeletal muscles during surgical or diagnostic procedures. The term *neuromuscular blocking agents* (NMBAs) is a cumbersome, but descriptive, name that refers to this class of drugs producing their effect by actions at the neuromuscular junction. The more general term *muscle relaxant* refers to any drug that has relaxant properties and would include centrally acting agents such as benzodiazepines, α_2-adrenoceptor agonists, and guaifenesin. Beneficial effects of NMBA administration during general anesthesia include facilitation of tracheal intubation, reduction of skeletal muscle tone at light planes of inhalant or injectable anesthesia, and prevention of patient movement during delicate ocular, neurological, or cardiac surgery. Although used frequently in human anesthesia and in some veterinary specialties such as ophthalmology, the use of NMBAs in general veterinary practice is limited. Inhalant anesthetics such as isoflurane are complete anesthetics in that they fulfill the *triad* of anesthesia: unconsciousness, analgesia, and muscle relaxation. All three of these properties are required in order to perform most invasive surgical procedures. Of the three properties of the triad, inhalant anesthetics are very good at producing loss of consciousness at comparatively light planes of anesthesia, whereas substantially deeper planes are required to obtund nociceptive processing and skeletal muscle contraction. Indeed, these last two properties are provided by potent inhalant anesthetics only by virtue of more profound depression of the central nervous system (CNS). Unfortunately, deeper planes of inhalant anesthetics are associated with a decrease in cardiovascular function; thus, the properties of muscle relaxation and analgesia are accompanied by reduced cardiovascular performance. In young, healthy animals having good cardiovascular reserve, this may be well tolerated; in patients having poor cardiovascular function, however, significant morbidity and mortality may result. Rather than using inhalant anesthetics to provide all three components of the triad, a safer approach may be one that uses lower concentrations of an inhalant to provide unconsciousness, an analgesic to inhibit nociceptive processing, and an NMBA to relax skeletal muscle. This approach has historically been termed *balanced anesthesia*. Balanced anesthetic techniques are frequently chosen because they provide optimal conditions for both the surgeon and the patient.

History of Muscle Relaxants

The introduction of NMBAs into anesthesiology in 1942 is a relatively recent event in medical practice. Indigenous South Americans had been using a paralyzing poison for centuries on the heads of their hunting arrows. This lethal compound was derived from the tropical plant *Chondodendron tomentosum* and caused paralysis and death to quarry that had been impaled by a coated arrow. Such a poison was an advantage because animals suffering a normally nonlethal wound would succumb and could be harvested by the hunter. The existence of this poison, known as curare, was recognized outside of South America, but its medical uses were not realized. The link was made when an explorer, Richard Gill, returned from the jungles of South America and was diagnosed with multiple sclerosis. The suggestion that the spastic paralysis might be relieved by administration of the arrow poison led Gill to overcome his disability and return to the South American jungle. He returned to the United States in the late 1930s having obtained a quantity of curare, which he sold to a pharmaceutical company that then purified the raw curare and marketed it under the trade name of Intocostrin. Initially, Intocostrin was used only in psychiatric medicine to control seizures that were associated with treatments of psychotic states. A physician in the company realized the potential the drug might have in the field of anesthesiology and convinced an anesthesiologist to undertake studies in humans. This was to be a monumental undertaking because the anesthesia community of the day was understandably not receptive to administration of a paralytic arrow poison to surgical patients. Indeed, the mere suggestion that one would administer a drug that would intentionally cause respiratory arrest was unthinkable to a generation of physicians who had grown up with the motto "Where there is breath, there is hope." Studies which suggested that d-tubocurarine, a quaternary alkaloid isolated from raw curare, was safe and useful for relaxing abdominal muscles during general anesthesia began to emerge, and use of the drug spread to Great Britain by 1945.[1] Another drug with paralytic properties similar to d-tubocurarine, but having the advantage of rapid onset and offset (succinylcholine), was introduced into human practice in the early 1950s.[2] Reports of the use of NMBA in dogs also began to appear in the early 1950s, and administration of succinylcholine to horses was described in the 1960s.[3,4] Both d-tubocurarine and succinylcholine have a number of undesirable cardiovascular effects. These agents can affect autonomic ganglia and cardiac muscarinic receptors, as well as induce histamine release. Although succinylcholine has the advantage of rapid onset and offset compared with d-tubocurarine, the additional disadvantages of hyperkalemia, arrhythmias, postanesthetic myalgia, and the changing nature of its block dictated that other NMBAs be developed.

Synthetic relaxants developed during the ensuing years included gallamine, decamethonium, alcuronium and, finally, steroid-based pancuronium. Most are now only of historical interest, although alcuronium is still frequently used in many parts of the world, and pancuronium serves as a parent molecule of several contemporary NMBAs. Atracurium and vecuronium, introduced in the 1980s, have the advantage of minimal to no car-

diovascular effects, minimal histamine release, and a controllable and predictable duration of action. Both are widely used in human anesthesia practice. Mivicurium, an analogue of atracurium with a rapid onset and brief action, was developed to take advantage of rapid onset of action in facilitating tracheal intubation after induction of anesthesia. It is essentially devoid of the problems of hyperkalemia, arrhythmia, and myalgia. Recently developed NMBAs include doxacurium, pipecuronium, and rocuronium, which represent an effort to produce an NMBA that has a precise, predictable duration of action and minimal untoward cardiovascular side effects.

Physiology of the Neuromuscular Junction

All muscle relaxants exert their effects at the *neuromuscular junction*, which forms the interface between the large myelinated motor nerve and the muscle that is supplied by that nerve. The neuromuscular junction itself may be divided into the prejunctional motor nerve ending, the synaptic cleft, and the postjunctional membrane of the skeletal muscle fiber. Present on the prejunctional and postjunctional areas of the neuromuscular junction are nicotinic receptors, which bind and respond to acetylcholine (ACh) or another suitable ligand. The prejunctional receptor is thought to be important in the synthesis and mobilization of ACh stores, but not for its release.[5] There appear to be two types of postjunctional receptors: junctional and extrajunctional.[6] The *junctional receptors* are found on the motor end plates of normal adult animals and are responsible for interacting with the released ACh, initiating muscle contraction. Antagonism of ACh at the junctional receptors is responsible for the relaxant effect seen when an NMBA is administered. The *extrajunctional receptors* are not present in high numbers on the skeletal muscle membranes of adult mammals, but are important because they are synthesized by muscles that are receiving a less than normal degree of motor nerve stimulation.[7] Thus, their number may be increased following spinal cord injury or after a period of muscle disuse, such as when a limb is cast. They are also present in neonates. The location of extrajunctional receptors is not restricted to the motor end plate and they may be located over the entire muscle cell surface.[8,9] Extrajunctional receptors appear to be more responsive to depolarizing NMBAs such as succinylcholine and less responsive to nondepolarizing NMBAs such as atracurium.[10] If the degree of neuromuscular deficit is severe, extrajunctional receptors may be more numerous and widely distributed over the muscle membrane. Such patients may have a more intense response to the actions of a depolarizing NMBA and a more profound release of intracellular potassium ions (K^+) with its concomitant adverse cardiac effects.[11]

The prejunctional nerve endings synthesize and store a quantity of ACh in synaptic vesicles. During normal neuromuscular transmission, an action potential arrives at the prejunctional motor nerve ending, causing depolarization of the nerve terminal. The depolarization of the nerve membrane activates adenylate cyclase, which converts adenosine triphosphate to cyclic adenosine monophosphate. The resultant conversion results in calcium-
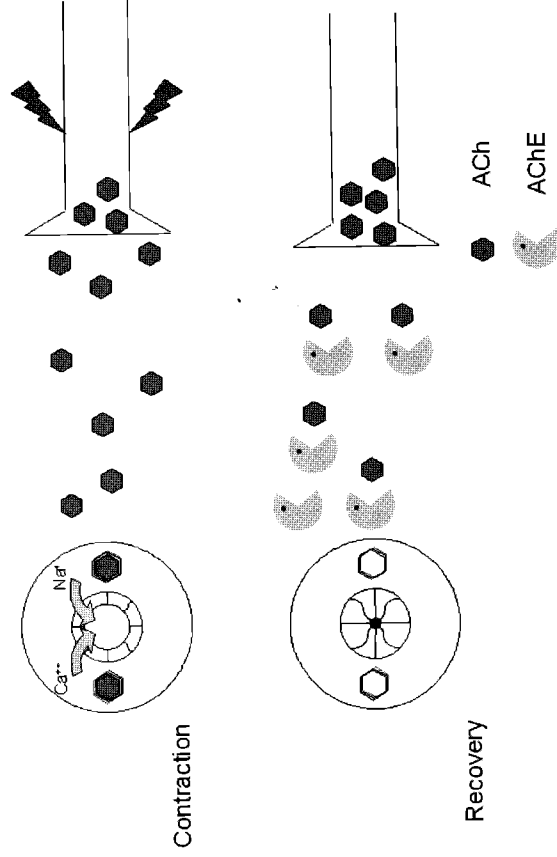
Neuromuscular Contraction

Contraction

Recovery

● ACh

🔶 AChE

Fig. 15.1. Top: Normal neuromuscular transmission. An action potential arriving at the motor end plate causes the release of acetylcholine (ACh) into the synaptic cleft. ACh binds to both postsynaptic receptors, which opens the ion channel and subsequent muscular contraction. **Bottom:** Recovery and repolarization occur when ACh is degraded by acetylcholinesterase (AChE), the receptor sites are cleared, and the ion channel closes. Ca^+, calcium ions; and Na^+, sodium ions.

ion (Ca^{2+}) entry into the nerve terminal and resultant release of ACh. ACh can then diffuse to the postsynaptic membrane and interact with postjunctional nicotinic receptors, resulting in the development of an end-plate potential (a muscle cell action potential) and ultimately muscular contraction (Fig. 15.1). ACh is rapidly hydrolyzed into choline and acetate by acetylcholinesterase. Thus, the muscle cell is depolarized by the end-plate potential created by the binding of ACh to the receptor and then is repolarized as the ACh is removed from the receptor and hydrolyzed.

The postjunctional receptors are concentrated on the end plate immediately opposite the sites of ACh release.[12] Electron microscopy of these receptors shows them to have a central pit surrounded by a raised circular area; thus, they look similar to a spool of thread that is viewed end on.[13,14] The raised circular area is the mouth of a cylinder of protein that protrudes through the cell membrane, and it contains the binding sites for ACh and other ligands. The pit is the extracellular opening of an ion channel that runs throughout the cylinder's length. The receptor is composed of five subunits of four distinct subunit types designated alpha, beta, gamma, and delta. The two alpha subunits of each receptor and the others are arranged into a cylinder having a potential space, the ion channel, contained within.[15] The functional opening of the channel is controlled by the ACh-binding sites present in the two alpha subunits. When two molecules of ACh are bound to the two binding sites on each of the two alpha subunits, the protein rotates into a new conformation and, in so doing, opens the ion channel and permits ion flow.[16] The open channel enables flow of small cations (sodium ions [Na^+] and Ca^{2+} flow in and K^+ flows out) but not large cations or anions. Ion-current flow depolarizes the postjunctional membrane.[17] As the ACh molecules dissociate from the nicotinic receptors and are hydrolyzed by acetylcholinesterase, the ion channel closes, current flow stops, and the membrane is repolarized.

Binding of ligands to the nicotinic receptor at the neuromuscular junction is competitive and reversible. Since two molecules of ACh bound to each of the receptor alpha subunits are required for normal function, antagonists have a distinct advantage in that they need only bind to one of the subunits to prevent normal neuromuscular transmission and thus paralysis.[18] The interaction of ACh and NMBA at the postjunctional receptors is a dynamic process of binding and dissociation and, coupled with the sheer number of receptors present (10,000 to 20,000/μm^2), the success or failure of neuromuscular transmission in the presence of an NMBA is determined by the concentration of the NMBA versus the concentration of ACh. A high percentage of receptors binding ACh favors muscular contraction, whereas a high percentage of receptors binding NMBA favors paralysis. This suggests a method for reversing paralysis induced by an NMBA. Increasing the concentration of ACh compared with the concentration of NMBA will increase the probability that the receptor will bind ACh and normal neuromuscular transmission will again result. Clinically, ACh concentration is increased by administration of inhibitors of acetylcholinesterase, such as neostigmine. When acetylcholinesterase is inhibited, ACh is not degraded immediately after release from the receptor, its half-life within the synapse is longer, and more of it is available to interact with receptors. Increased ACh activity is also seen as the concentration of an NMBA declines due to degradation of the drug. As the concentration declines, the competitive balance favors ACh and more normal neuromuscular transmission returns.

Pharmacology

Ligand-Receptor Interactions

The classic mechanism of action of an NMBA such as d-tubocurarine or atracurium is the competitive binding of the drug to the receptor thus blocking transmission of the nerve action po-

tential. There are at least two other less well understood mechanisms: desensitization and channel blockade.

Earlier it was stated that the cholinergic receptor is inactive with its potential ion channel collapsed when two molecules of ACh are not attached to the alpha subunits of the receptor. Binding of ACh to each of the two alpha subunits of the receptor causes the conformational change to the active state and enables the ion channel to open. However, the channel does not have to exist only in the open or collapsed state. A third possible conformation is the desensitized state, in which receptors bind ACh to the alpha subunits, but a conformational change and channel opening do not occur. A number of drugs, including agonists, antagonists, and inhalant anesthetics, appear to be able to switch the cholinergic receptor to the desensitized state. The desensitized-state hypothesis explains the synergistic action that inhalant anesthetics have with NMBAs because it is known clinically that much lower doses of NMBAs achieve an acceptable degree of relaxation when a patient is anesthetized with a volatile anesthetic. A large number of drugs may cause or promote desensitization, such as succinylcholine, thiopental, Ca^{2+}-channel blockers, local anesthetics, phenothiazines, cyclohexamines, inhalant anesthetics, and some antibiotics.[19-22]

Channel blockade occurs when a molecule becomes stuck within the channel, obstructing normal ion flux. This is possible because the mouth of the ion channel is much wider than the transmembrane portion, which enables molecules to enter the channel but not necessarily pass completely through it. Therefore, channel blockade blocks normal neuromuscular transmission not by competing for binding sites on the nicotinic receptor, but by interfering with the depolarization process in response to binding of an agonist.[23,24] This is an important distinction because the paralysis induced by channel blockade may not be antagonized by administration of an anticholinesterase. In fact, inhibition of cholinesterase enzyme may intensify the block because the opening of more ion channels in response to a greater concentration of ACh may provide a greater opportunity for the offending molecules to become trapped within the channel. It is known that many drugs can cause channel blockade, but the fact that NMBAs themselves can block the neuromuscular receptor channels may partially explain why administration of an anticholinesterase drug in an effort to antagonize neuromuscular blockade may sometimes intensify rather than lessen the paralysis.[25,26]

Depolarizing and Nondepolarizing Drugs

Depolarizing and nondepolarizing neuromuscular junction—blocking drugs both have an affinity for, and bind to, nicotinic ACh receptors at the neuromuscular junction; however, their intrinsic activity at the receptor is very different. Nondepolarizing drugs bind to the receptor but do not activate it (Fig. 15.2). Their onset of action is characterized by a progressive weakening of muscle contraction and, ultimately, flaccid paralysis. Depolarizing drugs also bind to the receptor and, similar to ACh, the receptor is stimulated, causing depolarization of the postjunctional membrane. Unlike ACh, succinylcholine and other depolarizing NMBAs are not susceptible to breakdown by acetylcholinesterase and thus the ion channel remains open and repo-

larization does not occur. The persistent state of depolarization associated with administration of depolarizing NMBAs causes inexcitability of the motor end plate and, as with nondepolarizing NMBA, a flaccid paralysis results. In addition to the differing mechanism of action of depolarizing drugs, several other differences are clinically apparent when comparing depolarizing and nondepolarizing NMBAs. Succinylcholine administration can cause muscle fasciculations immediately prior to the development of flaccid paralysis. Large doses, repeated administration, or administration of succinylcholine as an infusion causes the character of the block to change from the aforementioned classic depolarizing action (i.e., phase I block) to a phase II block which resembles that of nondepolarizing drugs such as d-tubocurarine. Despite years of investigation into the genesis of phase II block, its mechanism is still not clearly understood. Prolonged exposure of the cholinergic receptors to the agonist succinylcholine likely causes receptor desensitization, channel blockade, or a combination of both. Both receptor desensitization and channel blockade have properties that would mimic those of the nondepolarizing NMBAs and thus would change the mechanism and nature of the succinylcholine-induced block.

Individual Neuromuscular Blocking Drugs

The NMBAs are quaternary ammonium compounds that mimic the quaternary nitrogen atom of ACh. They are attracted to the nicotinic receptors at the motor end plate, as well as to nicotinic receptors located in autonomic ganglia. Most NMBAs are positively charged, water-soluble compounds that have a limited volume of distribution and, in many cases, limited hepatic biotransformation.[27] The water-soluble nature of these compounds suggests their pharmacokinetics differ markedly from those of most anesthetic drugs, such as thiopental and propofol. A hallmark of lipid-soluble anesthetic agents is their rapid onset of action and their rapid termination of effect after intravenous administration.

In contrast, the low lipid solubility exhibited by the NMBAs limits drug transfer across membrane structures, including the placenta and blood-brain barrier. Hepatic metabolism and redistribution to sites other than the skeletal muscles are not major mechanisms in the termination of NMBA effects. An exception is vecuronium, where biliary excretion is important in its elimination from the body.[28] Because of their water solubility, most NMBAs are excreted by glomerular filtration and are generally not reabsorbed by the renal tubules. The water-soluble nature of these drugs may also contribute to the observation that neonates may require relatively higher doses of NMBAs because neonates have a higher percentage of body water than do adults and typically higher apparent volumes of distribution for water-soluble drugs. Recommended doses of muscle relaxants used in common domesticated species are listed in Table 15.1.

Succinylcholine

This is currently the only depolarizing NMBA used in veterinary medicine. Structurally, the succinylcholine molecule is two ACh molecules joined end to end. This drug is rapidly hydrolyzed in

Neuromuscular Blockade
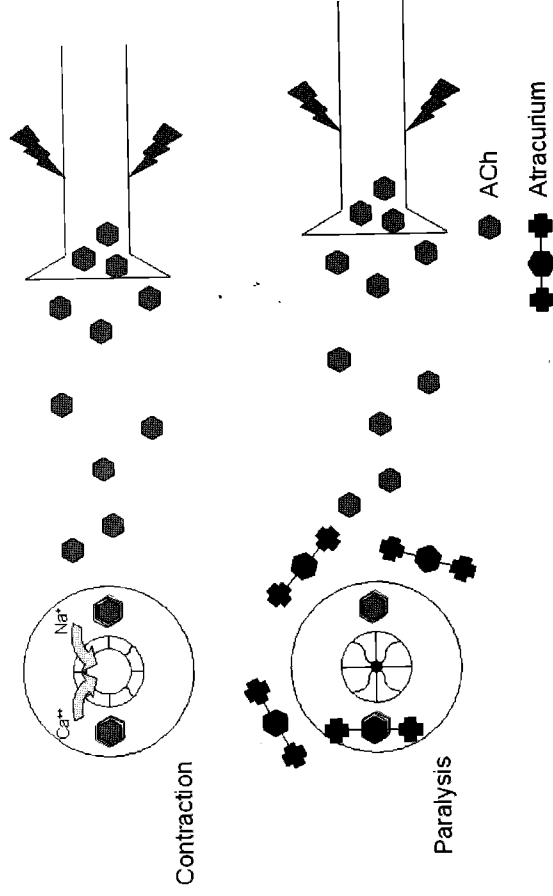

Contraction

Paralysis

● ACh

● ● Atracurium

Fig. 15.2. **Top:** Normal neuromuscular transmission proceeds as described in Fig. 15.1. **Bottom:** Atracurium competes with acetylcholine (ACh) at the postsynaptic receptor. The occupation of at least one of the two receptor sites by atracurium prevents receptor activation, and the ion channel remains closed. Ca$^+$, calcium ions; and Na$^+$, sodium ions.

Table 15.1. Doses of commonly used neuromuscular blocking agents in some domestic species.

Drug (mg/kg)	Dog	Cat	Horse
Succinylcholine	0.3–0.4	0.2	0.12–0.15
Pancuronium	0.07	0.06	0.12
Atracurium	0.15–0.2	0.15–0.25	0.07–0.15
Vecuronium	0.1–0.2	0.025–0.05	0.1
Pipecuronium	0.05	0.003	

plasma by pseudocholinesterase (plasma cholinesterase), so only a small fraction of the injected dose survives degradation in plasma to reach the site of action at the neuromuscular junction. Very little pseudocholinesterase is present in the synaptic cleft, so succinylcholine-induced paralysis is terminated by diffusion of the drug away from the neuromuscular junction and into the extracellular fluid. Paradoxically, the rapid degradation of succinylcholine in the plasma is in some way responsible for the rapid onset of effect achieved by the drug. Because of the rapid degradation by plasma pseudocholinesterase, comparatively large doses of succinylcholine may be administered without worry of an increased duration of effect. The higher the succinylcholine dose, the more rapid the onset of paralysis will be. This strategy does not apply when using nondepolarizing NMBAs, where a significant increase in the duration of action will follow increased dosages. Because of its rapid onset of effect and brief action, succinylcholine is often the relaxant of choice to facilitate rapid human endotracheal intubation. Use of NMBAs to facilitate endotracheal tube placement is not common in veterinary practice because, with the arguable exception of cats and pigs, laryngeal contraction is rarely an impediment to tracheal intuba-

tion. Pseudocholinesterase is synthesized in the liver, and production is decreased by liver disease, chronic anemia, malnutrition, burns, pregnancy, cytotoxic drugs, metoclopramide, and cholinesterase-inhibitor drugs.[29-32] Additionally, species differences in pseudocholinesterase activity may exist. A reduction in plasma cholinesterase activity can be expected to prolong the action of succinylcholine. Administration of organophosphate insecticides, such as dichlorvos and trichlorfon, to horses has been shown to reduce pseudocholinesterase activity and prolong the duration of succinylcholine-induced neuromuscular blockade.[33] Conversely, cats wearing a dichlorvos flea collar had no increased duration of succinylcholine effect.[34]

Pancuronium

This was the first in a series of nondepolarizing NMBAs having a steroid nucleus. The drug has a dose-dependent onset of approximately 5 min and action ranging from 40 to 60 min in dogs. A large fraction of the drug is excreted by the kidney, and the remainder is metabolized by the liver. As may be expected, the action lasts longer in patients with renal insufficiency. In addition to having affinity for the nicotinic receptors at the neuromuscular junction, pancuronium can also inhibit cardiac muscarinic receptors, thus mildly to moderately increasing heart rate in some patients. This effect appears to vary among species. The muscarinic receptor-blocking effect and associated increase in heart rate appear to be caused by a second positive charge attached to the steroid ring. Removal of a single methyl group and, thus, of the positive charge, creates vecuronium, which is devoid of these cardiovascular effects.

Atracurium

This is a short-acting nondepolarizing NMBA having a benzylisoquinoline structure similar to that of d-tubocurarine. The

drug has a dose-dependent onset of action of approximately 5 min, and its action lasts approximately 30 min in dogs. Repeated doses do not tend to be cumulative, so neuromuscular blockade is sometimes maintained via continuous intravenous infusion. Atracurium is unique in that almost half of it is degraded by Hofmann elimination and nonspecific ester hydrolysis. The remaining fraction is degraded by as yet undefined routes, although evidence exists that its action is not prolonged in people in hepatic or renal failure.[35,36] Hepatic metabolism and renal excretion are not necessary for termination of effect. Consequently, atracurium may be administered to patients with hepatic or renal insufficiency without significantly increasing its duration of action.

Hofmann elimination is a process of spontaneous molecular decomposition and appears to be pH and temperature dependent. It does not require enzymatic activity. Because Hofmann elimination may occur ex vivo, atracurium should be kept refrigerated and is supplied at a pH of 3.25 to 3.65. When injected intravenously, it spontaneously decomposes into laudanosine and a quaternary monoacrylate at physiological pH and temperature. The laudanosine metabolite is a known CNS stimulant and can induce seizures. Unlike atracurium, laudanosine is almost totally dependent on hepatic biotransformation for elimination; thus, laudanosine plasma concentrations may be elevated in patients who have hepatic insufficiency and are given atracurium for longer surgical procedures. Laudanosine-induced CNS stimulation and seizures are unlikely unless atracurium is administered for prolonged periods, as might occur in intensive care settings. Since Hofmann elimination is pH and temperature dependent, hypothermia may increase the duration of atracurium neuromuscular blockade and require a decrease in the infusion rate necessary to maintain neuromuscular blockade.[37] Ester hydrolysis of atracurium is accomplished by several plasma esterases unrelated to plasma cholinesterase. In contrast to succinylcholine metabolism, the duration of action of atracurium is not prolonged in the presence of cholinesterase inhibitors.

Many NMBAs having the benzylisoquinoline structure are associated with histamine release and a varying degree of hypotension. d-Tubocurarine, the prototypical benzylisoquinoline NMBA, is among the most potent at releasing histamine, but newer drugs having the benzylisoquinoline structure, such as atracurium and mivacurium, require several times the effective dose for neuromuscular blockade before appreciable amounts of histamine are released.[38,39] Although signs of histamine release, such as hypotension and tachycardia, are not usually observed when atracurium is administered, slow intravenous administration is always preferred.

Cisatracurium

Atracurium is a racemic mixture of ten optical isomers. The 1R-cis, 1R'-cis isomer, or cisatracurium, comprises approximately 15% of racemic atracurium, is approximately four times more potent, and has much less potential for histamine release. For example, in cats, plasma histamine concentrations were unchanged when up to 60 times the effective dose of cisatracurium was administered.[40] Cisatracurium has a similar onset time and duration of action to atracurium. Hofmann elimination metabolizes more than half the administered dose of cisatracurium, but, unlike with the racemic compound, ester hydrolysis does not occur. As with atracurium, Hofmann elimination causes laudanosine production. Since cisatracurium is approximately fourfold as potent as atracurium, the administered dose is correspondingly less, as is production of laudanosine.[41]

Vecuronium

Introduced in the 1980s, this was one of the first NMBAs free of cardiovascular effects. The discovery that the vagolytic properties and associated tachycardia seen with pancuronium administration were caused by two positive charges within the steroid molecule led investigators to remove a single methyl group from the parent pancuronium molecule. Vecuronium, the resultant drug, has remarkable cardiovascular stability and does not induce tachycardia nor release histamine.[42] This drug has a dose-dependent onset of action of approximately 5 min and an intermediate duration of action similar to that of atracurium: 30 min. As with atracurium, a cumulative effect with subsequent doses is not a prominent feature of this drug. Vecuronium is unstable when prepared in solution and is supplied as a lyophilized powder that is reconstituted with sterile water prior to injection. The powder does not need refrigeration, and, once reconstituted, the solution is stable for 24 h. Slightly more than half of the drug is metabolized by hepatic microsomal enzymes and excreted in the bile while a significant fraction undergoes renal elimination.[43] In humans, the action of vecuronium is either slightly prolonged or unchanged in patients who exhibit renal insufficiency but not in patients who suffer hepatic failure unless increased doses are administered.[44]

Rocuronium

This is a derivative of vecuronium, having approximately one-eighth the potency of the parent compound. Since vecuronium and rocuronium have similar molecular weights and rocuronium has lower potency, a higher injected dose of rocuronium places a greater number of molecules near the neuromuscular junction translating into a more rapid onset of neuromuscular blockade. The rapid onset of effect of rocuronium makes the drug an attractive nondepolarizing alternative to succinylcholine for tracheal intubation. Its duration of action in dogs is similar to that of vecuronium and atracurium.[45] Similar to vecuronium, rocuronium seems to be without cardiovascular effects and does not release histamine.[46] The primary route of elimination is via the hepatic system while a small fraction is eliminated via the kidney.[42]

Doxacurium

This is a very potent benzylisoquinoline NMBA with a long duration of action.[47] Similar to other benzylisoquinoline NMBAs, such as atracurium, doxacurium does not have vagolytic properties or cause ganglion blockade. Similar to cisatracurium, administration of clinical doses does not cause appreciable histamine release. Doxacurium appears to be minimally metabolized and is excreted unchanged into the bile and urine.

Mivacurium

This drug is a rapid-acting, short-duration NMBA marketed for use in humans for facilitating tracheal intubation at anesthetic induction. Similar to atracurium, mivacurium can induce histamine release if high doses are administered. Mivacurium is rapidly biotransformed by plasma pseudocholinesterase, and metabolites do not have appreciable neuromuscular blocking activity. Its dose-dependent duration of action differs between species. The action of typical doses used in humans lasts approximately 25 min, about one-half to one-third less than that of atracurium. Mivacurium also shows marked differences in potency among species, being much more potent in dogs than in people. In dogs, one-third of the human dose is associated with blockade that is five times longer.[48] The differences in duration of action between species may in part reflect the reduced activity of pseudocholinesterase in dogs, because normal plasma cholinesterase concentrations for dogs are reportedly from 19% to 76% of human values.[49] Also, canine pseudocholinesterase enzyme might have differing affinity for the three primary isomers of mivacurium.[49] Clinical observations indicate that mivacurium has a much briefer action in cats than in dogs.

Nonneuromuscular Effects

The NMBAs primary action is at the nicotinic receptors at the motor nerve plate, but most drugs affect other cholinergic receptors, including the cardiac muscarinic receptors and nicotinic ganglionic receptors within the autonomic nervous system. Many undesirable effects can be caused by either the blocking of receptors or the mimicking actions of ACh.

Cardiovascular Effects

ACh is the primary neurotransmitter of preganglionic and postganglionic neurons within the parasympathetic nervous system, whereas the sympathetic nervous system employs ACh only as a preganglionic neurotransmitter in most tissues. The ubiquitous presence of ACh and the structural similarities between ACh and the NMBAs provides an opportunity to induce physiological effects other than paralytic actions. Agonist or antagonist action at cardiac muscarinic receptors or nicotinic receptors at sympathetic ganglia may decrease or increase heart rate and cause cardiac dysrhythmias. Succinylcholine can mimic the effect of ACh at cardiac muscarinic receptors, leading to sinus bradycardia, junctional rhythms, and even sinus arrest.[50,51] Alternatively, by virtue of its ACh-like effects at sympathetic ganglia, administration of succinylcholine may increase heart rate and blood pressure.[52] The net clinical effect observed in an individual animal is probably a function of the species, dose, and timing of administration.

Nondepolarizing drugs, particularly the older agents, may also influence a patient's cardiovascular status. The rapid intravenous injection of a paralyzing dose of d-tubocurarine can decrease blood pressure significantly. This may occur by blocking the action of ACh at sympathetic ganglia, which then decreases sympathetic efferent activity, leading to hypotension. Alternatively, histamine release associated with the rapid intravenous adminis-

tration of d-tubocurarine could cause hypotension. This mechanism probably causes the majority of hypotension, because either slow intravenous administration, or prior administration of an antihistamine, usually attenuates the response.[53]

Rapid intravenous administration of clinically used doses of pancuronium may produce an increase in heart rate and corresponding increases in arterial pressure and cardiac output.[54,55] This response is caused by blockade of cardiac muscarinic receptors and resultant decreased parasympathetic nervous system effects on the heart.[56] In addition, there is evidence that pancuronium may stimulate the release of norepinephrine from sympathetic adrenergic nerves.[57] A modest increase in heart rate is not always disadvantageous, particularly when drugs having vagomimetic effects (e.g., opioids and α_2-adrenergic agonists) are concurrently administered to a patient. The ability of pancuronium to increase heart rate is inconsistent among species, however. In dogs, heart rate, blood pressure, and cardiac output typically increase.[55,56] Heart rate does not change in horses anesthetized with halothane and administered pancuronium, whereas both heart rate and blood pressure may increase in ponies.[58,59] Pancuronium administration does not change heart rate or blood pressure in anesthetized calves, but increases heart rate and blood pressure in pigs.[60,61] The newer, intermediate-duration agents, such as atracurium and vecuronium, are virtually devoid of these cardiovascular effects. Atracurium and mivacurium may release histamine, but blood pressure is rarely decreased when modest doses of these NMBAs are used.

The newest NMBAs—pipecuronium, doxacurium, and rocuronium—were designed with cardiovascular stability in mind and their administration is unlikely to be associated with profound changes in cardiovascular function. Rapacuronium induces histamine release, but this is minimized if rapid intravenous administration is avoided.[62]

Histamine Release

The quaternary ammonium structure inherent in the NMBAs is responsible for the propensity of many of these compounds to stimulate histamine release following intravenous injection. Release of histamine in animals causes vasodilation, a decrease in blood pressure, and possibly a compensatory increase in heart rate. Histamine release is usually associated with administration of the benzylisoquinoline class of NMBAs but has been reported with low-potency steroid relaxants.[63] Because d-tubocurarine is a potent inducer of histamine release at doses required to produce clinically useful neuromuscular block, vasodilation and increased heart rate are commonly encountered.[54] For newer NMBAs, the dose necessary to evoke clinically significant histamine release is much higher than the dose necessary to produce relaxation. For example, in people, approximately 2.5 times the effective dose of atracurium is required to stimulate histamine release.[64] Pretreatment of patients with H_1-receptor and H_2-receptor antagonists is effective in preventing the cardiovascular effects associated with NMBA-induced histamine release.[65] Worries about histamine release with newer NMBAs may be avoided simply by administering relaxants more slowly and refraining from administering higher doses.

Placental Transfer

All clinically used NMBAs are large, hydrophilic, polar molecules. As a consequence, their transfer across cell membranes, including the placenta, is limited. At clinical doses, placental transfer of relaxants is minimal and effects on the neonate are unlikely. There is widespread use of NMBAs during human cesarean operations, and atracurium and succinylcholine have been used clinically in small and large domestic animals without consequence to neonates. Administration of NMBAs—such as pancuronium, succinylcholine, gallamine, and d-tubocurarine—to pregnant ferrets and cats does not impair muscle-twitch strength in neonates.[66]

Central Nervous System Effects

Being large, polar, hydrophilic, polar molecules, the NMBAs do not cross cell membranes readily, but evidence exists that most of these drugs do gain limited entrance into the cerebrospinal fluid and may be associated with CNS effects. Pancuronium administration reportedly reduced the minimum alveolar concentration of halothane in humans.[67] However, a subsequent study in humans found that pancuronium, atracurium, or vecuronium administration had no effect on the minimum alveolar concentration (MAC) of halothane.[68] Accidental administration of NMBAs into the cerebrospinal fluid has caused myotonia, autonomic effects, and seizures.[69,70] Laudanosine, a metabolite of atracurium, easily crosses the blood-brain barrier in dogs, and high concentrations may stimulate the CNS.[71] Clinically useful dosages of atracurium, however, are unlikely to result in the formation of a sufficient quantity of laudanosine to alter the CNS.

Protein Binding

All nondepolarizing NMBAs are protein bound, but the clinical significance of such binding is unclear. Presumably, only the unbound fraction of drug is available to interact at ACh receptors and induce paralysis. In studies of people who had hepatic cirrhosis with decreased plasma protein concentrations, the proportion of d-tubocurarine, pancuronium, and vecuronium bound to plasma protein was not different compared with healthy patients who had normal plasma protein concentrations.[72,73] Thus, despite the theoretical concerns of low plasma protein increasing the proportion of free, active drug, the amount of NMBA that is protein bound in hypoproteinemic patients appears to remain unchanged.

Nonneuromuscular Effects of Succinylcholine

Several, often undesirable, nonneuromuscular side effects are associated with the administration of succinylcholine. These sequelae include hyperkalemia; increased intraocular, intracranial, and intragastric pressure; and muscle soreness.

Hyperkalemia

Succinylcholine administration is associated with a transient increase in serum potassium levels. Succinylcholine activates the nicotinic motor end-plate receptors but, unlike ACh, is not immediately degraded by acetylcholinesterase. This produces depolarization characterized by open ion channels that enable potassium ions to egress from the muscle fiber into the extracellular space. As a result, serum potassium concentrations can rise transiently after drug administration. In healthy patients, this increase is usually without adverse effects, provided that cardiovascular disease is not present and preadministration serum potassium levels are normal. In patients with burns, severe muscle trauma, muscular denervation, nerve damage, or neuromuscular disease, extrajunctional ACh receptors proliferate over the surface of the muscle fiber. This increase in receptor density is accompanied by an increase in sensitivity to the depolarizing muscle relaxants and an increase in the amount of intracellular potassium released in response to succinylcholine administration. The increase in extrajunctional ACh receptor density begins to occur within 2 days after the injury and can persist for 2 to 3 months.[74]

Intraocular Pressure

Succinylcholine administration increases intraocular pressure. In humans, intraocular pressure usually peaks within 2 to 4 min and remains increased for at least 6 min after administration.[75] The mechanism responsible for the increase in intraocular pressure is presently unknown but likely involves altered circulation to the eye. The administration of the calcium-channel blocker nifedipine attenuates this increase.[76] Administration of succinylcholine to patients who have penetrating eye injuries should be avoided because it can cause ocular evisceration. Controversy exists as to whether administration of a nondepolarizing NMBA prior to succinylcholine prevents increases in intraocular pressure. It is important to realize that the use of any induction technique that might cause gagging or forceful coughing will raise intraocular and intracranial pressure and thus must be avoided in patients who have an open globe. Induction with a rapid-acting injectable anesthetic and being certain that adequate anesthetic depth has been achieved prior to attempting tracheal intubation are critical in preventing intraocular pressure increases.

Intragastric Pressure

Because succinylcholine administration causes muscle contraction that manifests clinically as fasciculations of the skeletal muscles, abdominal constriction and increases in intraabdominal and intragastric pressure can occur, increasing the potential for regurgitation.

Intracranial Pressure

Muscle fasciculations induced by succinylcholine may also increase intracranial pressure. In humans, prior administration of a nondepolarizing NMBA prevents the increase in intracranial pressure. Since most domestic animals can be easily intubated without use of an NMBA, it is recommended that succinylcholine be avoided in patients with intracranial hypertension. As with penetrating eye injuries, a rapid, smooth induction of anesthesia is a more desirable strategy in preventing unnecessary increases in intracranial pressure.

Muscle Responses

Succinylcholine administration is often associated with muscle soreness. Myalgia results from muscle fasciculations that occur

during the initial depolarization of the motor end plate.[77] The intensity of the fasciculations and the intensity of muscle pain are correlated.[78] Although skeletal muscle enzymes such as creatine kinase increase after succinylcholine administration, whether animals experience muscle pain similar to that of humans is unknown, but likely.[79-81]

Muscle Relaxants in Anesthetized Animals

The use of muscle relaxants in veterinary practice is not as frequent as in human medicine. Human patients are frequently given muscle relaxants to facilitate endotracheal intubation and surgical access. Most animals can be intubated relatively easily without paralysis, and muscle relaxation caused by inhalant anesthetic agents is adequate for most procedures. Because of the need for familiarity with NMBA pharmacology and mechanical ventilation, the use of muscle relaxants in animals has been limited mostly to teaching hospitals and adequately equipped specialty practices and research institutions.

Indications

Muscle relaxants may be administered for numerous reasons. To facilitate intubation, muscle relaxants are typically given with hypnotic drugs to eliminate laryngeal spasm and provide rapid control of the airway. The need for a motionless, centrally positioned eye during intraocular or corneal surgery often requires the use of a muscle relaxant. Other indications include prevention of unconscious spontaneous movement, reduced resistance to controlled ventilation, and facilitation of surgical access during surgery.

Precautions

Because the muscles of respiration are paralyzed, ventilation must be controlled, either by a mechanical ventilator or by a staff member who can manually ventilate the patient until muscle strength is restored. Muscle relaxants have no sedative, anesthetic, or analgesic properties, so it is critical that the animal be adequately anesthetized to render it completely unconscious. Assessing the level of anesthesia in a paralyzed patient is more difficult than in a nonparalyzed patient because the usual indicators of depth (e.g., purposeful movement in response to a noxious stimulus, palpebral response, and jaw tone) are abolished. When including an NMBA in an anesthetic protocol, anesthetists must be certain they can reliably maintain an adequate plane of surgical anesthesia and level of ventilation.

Historically, muscle relaxants have been given alone to animals for capture or restraint, including use as the sole agent for brief surgical procedures (e.g., equine castration). At this time, the use of such inhumane practices is not justified because of the widespread availability of safe and effective anesthetics. The administration of an NMBA alone to an awake patient for immobilization purposes is also considered inhumane.

Selection

When choosing a muscle relaxant, one must consider many factors, including the species to be paralyzed, the reason for paraly-

sis, the duration of action required, the health status of the patient, and concurrent drug administration. Relaxants will differ in the onset of action, duration of action, recovery time, cardiovascular effects, and route of elimination. If a rapid onset and brief action are needed, the choice might be rocuronium or mivacurium, whereas doxacurium may be selected for longer action without significant cardiovascular effects. Atracurium is metabolized via Hofmann elimination and may be a good choice when hepatic or renal disease is present.[35,36]

Because many factors will affect the intensity and duration of muscle paralysis, monitoring of neuromuscular blockade is useful for titrating the dose needed for the desired effect. It is important to remember that individual muscle groups respond differently to muscle relaxants. The diaphragm is less sensitive to the effects of muscle relaxants compared with the muscles of the limbs.[82] Therefore, a higher dose may be required to abolish spontaneous ventilation compared with the dose for facilitation of fracture reduction. In horses, when a dose of muscle relaxant required to abolish the hoof twitch is administered, the facial twitch will often remain, though at reduced strength.[83,84] When not monitoring hoof-twitch tension, it should be appreciated that the facial twitch may be present even when adequate relaxation has been achieved in the limb for performing the surgical procedure.

Factors Affecting Neuromuscular Blockade

A number of factors can influence the duration of action, intensity, and recovery from neuromuscular blockade. Whenever a muscle relaxant is administered, neuromuscular function must be monitored during the anesthetic and recovery periods to avoid overdosing and residual paralysis.

Impaired Metabolism and Excretion

Hepatic failure may alter the initial effect of nondepolarizing muscle relaxants because of an increase in the volume of distribution. However, their effect may be increased from decreased metabolism, especially when drugs dependent on hepatic biotransformation (e.g., vecuronium) are administered.[85-87] Impaired liver function may also prolong or cause residual neuromuscular blockade.[88] In general, muscle relaxants are not highly protein bound to albumin, typically less than 50% bound.[89-92] Thus, the net effect of low albumin may not be clinically significant. Decreased esterase activity may slow the biotransformation of mivacurium and atracurium. Patients with biliary obstruction may have reduced hepatic clearance of muscle relaxants.[93] The clinical impact of hepatic failure depends on the specific NMBA and dose administered.

In patients with renal insufficiency, paralysis may be prolonged when muscle relaxants that rely predominantly on renal elimination (gallamine, pancuronium, or doxacurium) are given.[94-97] Recovery from mivacurium administration may also be prolonged, possibly because of decreased pseudocholinesterase activity.[98] Atracurium pharmacokinetics are generally unaffected, but if a constant-rate infusion is given to a patient with renal failure, laudanosine may accumulate.[99] It is best to avoid

the use of high doses, repeated doses, or continuous infusions of muscle relaxants that primarily depend on renal elimination in patients with significant renal disease.

Anesthetic Drugs

Inhalant anesthetic agents cause a time and dose-dependent enhancement of the intensity and duration of block produced by muscle relaxants.[100] The explanation for this interaction is complex, with inhalational agents suppressing motor evoked potentials in response to spinal cord and transcranial stimulation. Muscle contractility is altered, and variation in regional muscle blood flow causes a greater fraction of the relaxant to reach the site of action.[101] The effects are greatest after administration of a long-acting relaxant or during a continuous infusion. The order of potency of some of the inhalational anesthetics in enhancing muscle relaxant effects is as follows: diethyl ether > enflurane > isoflurane > desflurane > halothane.[101] Also, antagonism of the block may be delayed, especially if inhalant anesthesia is continued after administration of the reversal agent. Monitoring of neuromuscular function helps to facilitate the appropriate dosing of muscle relaxants during inhalational anesthesia.

Most injectable anesthetic agents have only minor effects on the neuromuscular blocking properties of muscle relaxants. Induction agents, such as thiopental, ketamine and propofol, may minimally enhance neuromuscular blockade.[101]

Acid-Base Disturbances

Generally, respiratory acidosis increases the intensity of muscle blockade, whereas respiratory alkalosis decreases the effect.[102-105] Both metabolic acidosis and alkalosis may potentiate the effects of muscle relaxants and make it more difficult to antagonize relaxant-induced muscle paralysis.[102,103,105,106]

Electrolyte Disturbances

Alterations in serum concentration of potassium, magnesium, and calcium influence neuromuscular blockade. Decreases in extracellular potassium result in hyperpolarization of the end plate and resistance to ACh-induced depolarization.[107] A relative increase in extracellular potassium lowers the resting membrane potential, opposing the effect of the muscle relaxant.[107] Increased serum magnesium concentrations compete with ionized calcium, decreasing ACh release. Accordingly, in patients given magnesium sulfate, the duration of action of muscle relaxants may increase.[108] Hypocalcemia decreases ACh release, muscle action potential, and muscle contraction strength, thus increasing the effect of the neuromuscular block.[107,109] Typically, hypercalcemia decreases the effect of d-tubocurarine, pancuronium, and possibly other NMBAs, resulting in a higher dose requirement to achieve paralysis.[107]

Hypothermia

This generally slows drug elimination and decreases nerve conduction and muscle contraction. The overall clinical effect will vary with the degree of hypothermia. Care is required when administering muscle relaxants in cold environments. Doses may need to be reduced to prevent prolonged paralysis.

Age

Youth is associated with altered dose requirements of muscle relaxants. Receptor immaturity and decreased clearance appears to increase the potency of muscle relaxants in the young.[110-112] On the other hand, very young animals may require higher doses of muscle relaxants because of increased extracellular fluid and a larger volume of distribution when compared with adults. In addition, in younger animals, muscle relaxants usually have a faster onset of action while neuromuscular function recovers more quickly, so a lower dose of antagonist is usually required at the termination of the procedure.[113]

Although the data from published studies are not always clear-cut, old age may be associated with an increase in the effect of muscle relaxants, perhaps because of a lower volume of distribution and decreased rate of clearance. In elderly human patients, a delay in reversal and the need for higher doses of reversal agents are common, and likely attributable to slower spontaneous recovery.[114,115]

Neuromuscular Disorders

Animals with neuromuscular disorders may exhibit unpredictable responses to both depolarizing and nondepolarizing muscle relaxants. Care should be taken when administering muscle relaxants to patients with neuromuscular disorders or a history of muscle weakness or wasting.

Peripheral neuropathies may be classified as idiopathic, familial, metabolic, or immune mediated. In human patients, peripheral neuropathy may increase the effect of nondepolarizing muscle relaxants because of neural damage and the possibility of denervation-induced upregulation.[116] These patients may also be predisposed to succinylcholine-induced hyperkalemia.[117]

Diseases such as tick paralysis and botulism impair presynaptic release of ACh. Patients with presynaptic neuromuscular disorders show an increased sensitivity to nondepolarizing muscle relaxants. Myasthenia gravis is an autoimmune disease that causes generalized muscle weakness from a decrease in the number of ACh receptors on the motor end-plate muscle membrane. ACh is released normally, but its effect on the postsynaptic membrane is reduced. Patients with myasthenia gravis may be resistant to succinylcholine-induced paralysis, but are extremely sensitive to nondepolarizing relaxants and have an increased sensitivity toward succinylcholine-induced phase II block.[118,119] Patients with myasthenia gravis do not appear to be more sensitive to succinylcholine-induced hyperkalemia or malignant hyperthermia.[120] From published reports of dogs with myasthenia gravis, the initial dose recommendations of atracurium and vecuronium are 0.1 mg/kg and 0.02 mg/kg, respectively.[121,122]

Antimicrobial and Other Drug Interactions

The most notable effects on neuromuscular blockade occur with the administration of polymyxin and aminoglycoside antimicrobials, but can also occur with tetracycline, lincomycin, and clindamycin. Polymyxins may depress postsynaptic sensitivity to ACh and enhance channel block.[123,124] Antagonism with either neostigmine or calcium may be difficult and unreliable.[124] Ami-
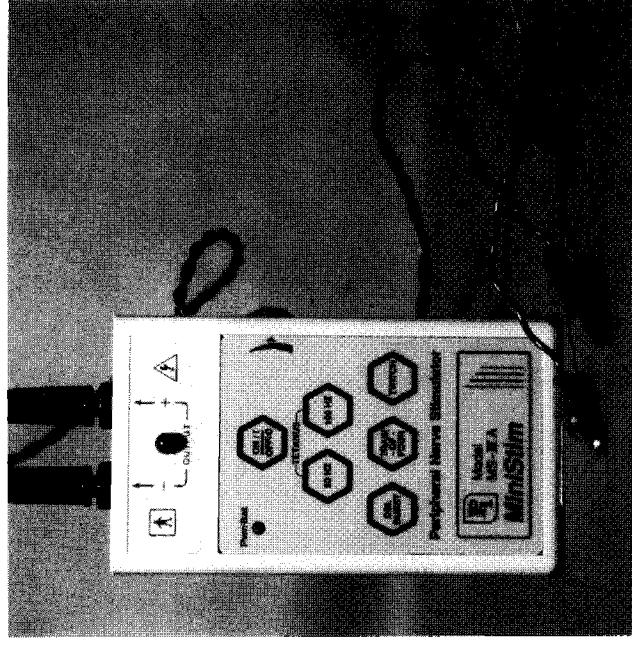
noglycosides, such as gentamicin, kanamycin, neomycin, streptomycin, and tobramycin, have a presynaptic site of action, as evidenced by depressed ACh release. The ability to antagonize blockade with calcium supports this mechanism and site of action.[124] Studies in anesthetized cats and horses given atracurium have shown a significant decrease in twitch tension after administration of gentamicin (2 mg/kg intravenously [IV]), but recovery times were not significantly changed.[125,126] Cats given gentamicin (10 mg/kg IV) during neuromuscular blockade have shown a significant decrease in tibialis cranialis twitch response.[127] Furthermore, dogs given a single daily dose of gentamicin (6 mg/kg IV as a bolus) had significantly decreased twitch tension, while recovery time did not differ from that for controls.[128]

Tetracycline administration presumably depresses ACh release through calcium chelation. The enhanced blockade is usually reversible with calcium, but not neostigmine, administration.[124] The primary site of the inhibitory action of lincomycin may be directly on the muscle. It may also have slight presynaptic and postsynaptic activity. This effect is poorly reversed with neostigmine or calcium but partially reversed with 4-aminopyridine.[124] Clindamycin has a greater neuromuscular blocking effect than lincomycin: The mechanism is direct inhibition of the muscle, and reversal is difficult with either calcium or neostigmine administration.[124] Penicillins and cephalosporins appear to have a negligible effect on overall neuromuscular function.[124] Nevertheless, whenever an antibiotic is administered to a patient also given a muscle relaxant, the possibility of an enhanced block and/or residual paralysis should be considered. Close patient monitoring is recommended well into the recovery period.

Lithium administration may also increase or prolong neuromuscular blockade by competing with sodium and decreasing ACh release. The effects of muscle relaxants have been potentiated by numerous classes of drugs, including beta blockers, doxapram, anticonvulsants, steroids, and H_2-receptor antagonists.[101]

Monitoring Neuromuscular Blockade

Neuromuscular function should be monitored whenever a muscle relaxant is administered. Appropriate monitoring will facilitate proper dosing of both the muscle relaxant and its antagonist. To prevent residual paralysis and muscle weakness in the recovery period, it is critical that monitoring be continued until the function is fully restored. Evoked motor responses to peripheral nerve stimulation are used to evaluate the degree of neuromuscular blockade. Many handheld peripheral nerve stimulators are available (Fig. 15.3).

Sites of Stimulation

Sites for stimulation of peripheral motor nerves in dogs and cats include the peroneal and ulnar nerves (Figs. 15.4 and 15.5). In horses, the facial nerve and superficial peroneal nerve are most commonly used (Figs. 15.6 and 15.7). Contact electrodes are placed over the nerve to be stimulated, and the resultant motor response is compared with the prerelaxant response.
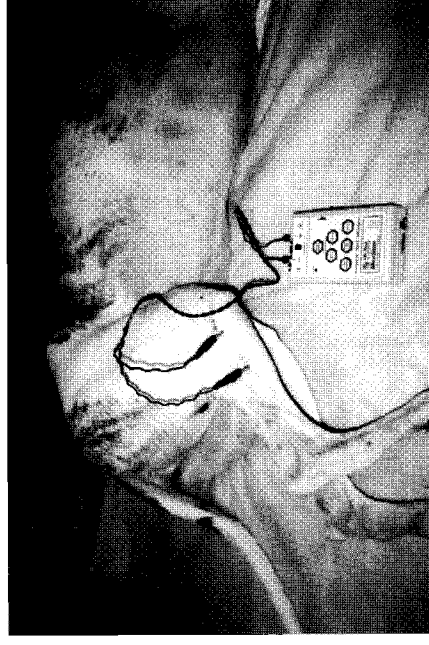

Fig. 15.3. Peripheral nerve stimulator.

Fig. 15.4. Superficial peroneal nerve stimulation in a dog.

Electrical Stimulation Characteristics

When monitoring neuromuscular function in veterinary patients, there are standard methods for stimulating peripheral nerves. The output from the peripheral nerve stimulator should be a square-wave stimulus lasting 0.2 to 0.3 ms. Ideally, the output current of the nerve stimulator should be adjustable, enabling a *supramaximal impulse* (i.e., a current slightly greater than that required to elicit the maximum motor response) to be applied to the nerve. A supramaximal stimulus ensures that all fibers in the nerve bundle are depolarized. Since muscle fibers contract in an all-or-none fashion, any subsequent changes in the evoked motor response during supramaximal stimulation of the peripheral nerve are caused by changes at the neuromuscular junction or muscle level, not by loss of nerve fiber input.
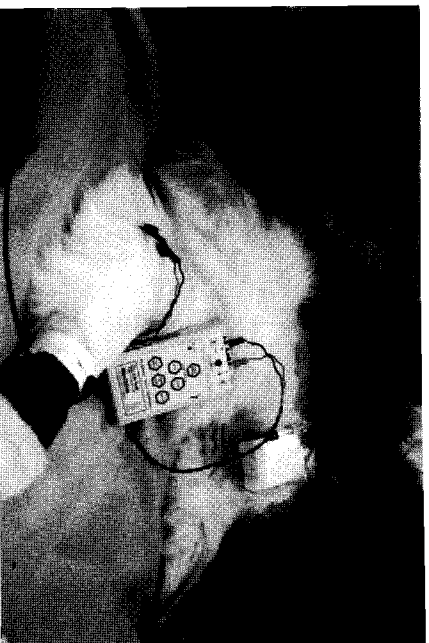
Fig. 15.5. Ulnar nerve stimulation in a dog.

Fig. 15.6. Facial nerve stimulation in a horse.

Fig. 15.7. Peroneal nerve stimulation in a horse.

Pattern of Stimulation

Ideally, the peripheral nerve stimulator should have a variable output and be capable of providing single-twitch, train-of-four, tetanic, and double-burst patterns of stimulation. Examples of the evoked muscle response to supramaximal stimulation before and after administration of a muscle relaxant are presented in Fig. 15.8. Partial neuromuscular block with depolarizing and nondepolarizing relaxants modifies the recorded responses to these stimulation patterns. These modified responses are summarized in Table 15.2.

Single Twitch

When using the single twitch, the simplest form of nerve stimulation, the degree of relaxation is assessed by dividing the elicited response by the prerelaxant response. The *prerelaxant response* is the twitch response measured immediately prior to the administration of the muscle relaxant. Since ACh release is decreased by the prejunctional effects of the relaxant, the frequency of single-twitch stimulation should be no greater than approximately one twitch every 7 to 10 s.[129] If the stimulus is applied too frequently, the resultant twitch response will be artificially low,

causing inaccuracy in determination of the degree of relaxation. Twitch response is not depressed until 75% to 80% of receptors are blocked and will be abolished when approximately 90% to 95% of receptors are blocked.[130]

Train of Four

The *train-of-four (TOF) pattern* of stimulation is the delivery of four supramaximal impulses over 2 s (2 Hz). The TOF can be repeated every 10 to 20 s without significant temporal effects. The relaxation level is determined by comparing the ratio of the intensity of the fourth twitch to the first twitch (T_4/T_1 ratio). Since the TOF serves as its own control, it is not necessary to determine baseline values prior to relaxant administration, although proper stimulator function should be verified before paralysis. In the absence of neuromuscular blockade, the T_4/T_1 ratio will be 1.0. After a nondepolarizing muscle relaxant is administered, when approximately 70% of receptors are occupied the twitches will fade, beginning with the fourth, followed by the third, second, and first twitches.[131] The dose of relaxant given will determine the degree of fade, the strength of any remaining twitches, and how long the twitches are absent. During recovery, the twitches will reappear in reverse order. A T_4/T_1 ratio of 0.7 or greater is associated with adequate clinical signs of recovery from the muscle relaxant.[132]

During the phase I block from a depolarizing relaxant, the TOF fade will be absent. However, repeat administration or continuous infusion of the depolarizing drug can cause a phase II block. When this occurs, fade will be seen following a TOF stimulus (Table 15.2).[133]

Tetanic Stimulation

Sustained muscle contraction is achieved by continuously delivering a high-frequency (50 Hz) supramaximal stimulus for 5 s.[133] Partial neuromuscular blockade from nondepolarizing relaxant administration will reduce tetanic height and cause fade.[134] Although this pattern of stimulation is helpful for detecting residual neuromuscular blockade during the anesthetic recovery period, it is important to remember that tetanic stimulation can be painful for lightly anesthetized or conscious patients.[135]
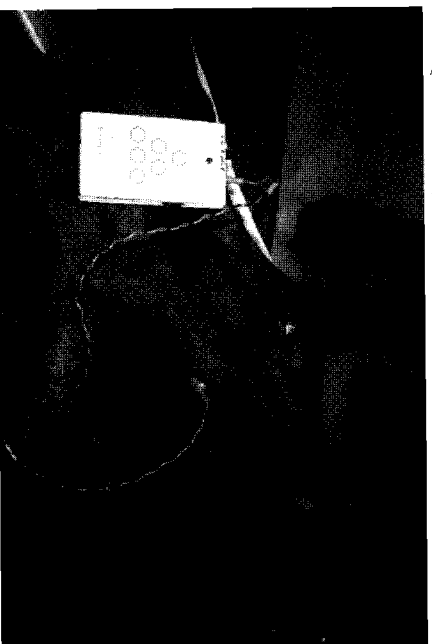
Table 15.2. Responses during partial neuromuscular block[a]

Criteria	Depolarizing Block	Nondepolarizing Block	Phase II Block
Fasciculation before onset of block	Yes	No	—
Time for onset	Short	Longer	—
Single twitch	Depressed	Depressed	Depressed
Tetanic height	Depressed	Depressed	Depressed
Tetanic fade	Minimal or absent	Present and marked	Present and marked
Train-of-four fade	Minimal or absent	Present and marked	Present and marked
Posttetanic facilitation	Minimal or absent	Present	Present
Response to anticholinesterases	Block is prolonged	Block is antagonized	Block is antagonized

[a]Distinguishing features of depolarizing, nondepolarizing, and succinylcholine–induced phase II block. The left column lists the different patterns of nerve stimulation or other characteristic, and the second, third, and fourth columns list the respective responses in the presence of partial neuromuscular block.

Posttetanic Facilitation

Posttetanic facilitation is an increase in an evoked response from a stimulus delivered shortly after tetanic stimulation. This is thought to be caused by increased ACh release from the nerve terminal, but other theories exist.[130] It is characterized by either an increase in twitch tension or a decrease in the degree of fade in response to either a single-twitch, TOF, or double-burst pattern of stimulation. Posttetanic facilitation is often the first clinical indicator of recovery from neuromuscular blockade.[136,137]

Double-Burst Stimulation

Double-burst stimulation (DBS) is the delivery of two minitetanic bursts, two to four impulses each, delivered at a rate of 50 Hz and 750 ms apart. When DBS is used, a ratio of the response to the second burst compared with the response to the first burst (D_2/D_1) is calculated. DBS may be superior to TOF because not only does DBS correlate highly to TOF when assessed via mechanomyography, but fade is more readily seen with DBS using both visual and tactile means.[130] An additional advantage
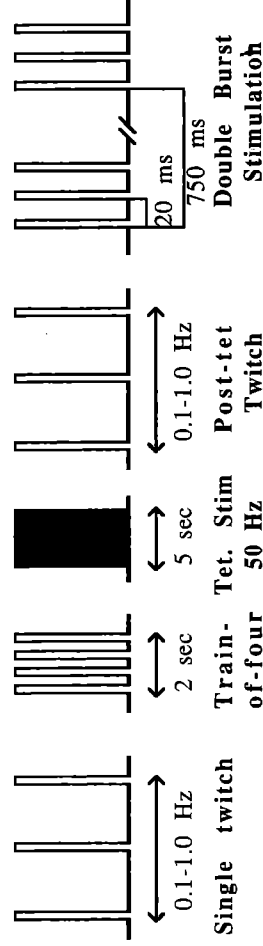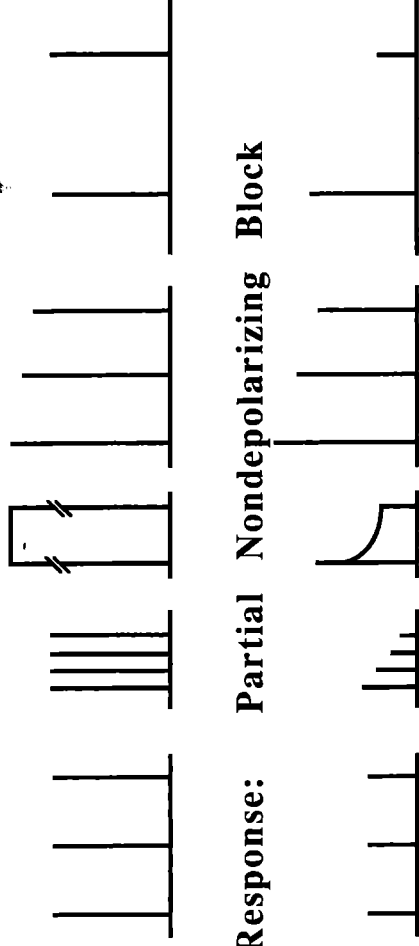

Fig. 15.8. Diagram showing different peripheral nerve stimulation patterns for monitoring neuromuscular function **(top panel)**. Under each pattern is shown the characteristics of the evoked muscle responses measured mechanically before **(center panel)** and during **(bottom panel)** partial block.

of DBS is that D$_1$ is detectable at a deeper level of neuromuscular blockade than is T$_1$.[138]

Quantifying Evoked Responses

Whenever a muscle relaxant is administered, neuromuscular function must be monitored until normal neuromuscular function is restored. Residual blockade during the recovery period can cause serious complications. Proper monitoring provides information about the degree and duration of neuromuscular blockade, and assures the observer that no residual blockade is present prior to recovery from anesthesia. In veterinary patients, the most common method used for assessing the degree of neuromuscular blockade is visual observation of the evoked response from peripheral nerve stimulation. With experienced observers, visual observation is adequate in most clinical situations. However, more accurate evaluation of the depth and duration, of block is best achieved when the muscle response is recorded and measured. The two methods for accurately quantifying the evoked response are mechanically recorded, where the twitch tension by the muscle is measured using a force displacement transducer, and electromyographically recorded, where the muscle action potential is measured.

Mechanomyography

Mechanomyography (MMG) measures the evoked response of the stimulated muscle by force translation. The use of this method has been described in cats, dogs, horses, ponies, cows, and llamas.[45,125,126,139-141] With the limb immobilized, stimulating electrodes are placed over a peripheral nerve (peroneal or ulnar). The force transducer is attached to a paw or hoof at a right angle to the direction of muscle contraction. For maximum evoked muscle-twitch tension, a resting tension of 100 to 300 g should be applied. A supramaximal stimulus is applied to the nerve by using a single-twitch, TOF, or double-burst stimulation pattern. The resultant twitch tension can then be quantified. By using MMG, the depth and duration of neuromuscular blockade can be determined accurately. However, limitations make its use in many clinical situations impractical. To prevent changes in resting tension and twitch angle, the limb must be immobilized and no movement should occur during the recording period.[142]

Electromyography

Electromyography (EMG) measures the compound action potential of muscle fibers contracting during a supramaximal stimulus of a peripheral motor nerve. With the stimulating electrodes placed over a peripheral nerve, the recording electrode is placed over the innervation zone of the muscle, midway between its origin and insertion. Also required are a reference electrode, placed over the insertion site, and a ground electrode, placed between the other two electrodes. EMG has the advantage of requiring less or no limb immobilization and no resting tension, and there are more choices as to which muscles may be used.[142] In a study in dogs given atracurium, there was no statistical difference between MMG and EMG during TOF stimulation for either T$_1$ or T$_4$/T$_1$.[143] The disadvantage of EMG is that it may be difficult to obtain proper electrode placement for accurate results, particularly in smaller patients. Until a standard method is developed and validated for various species and sites of monitoring, MMG will remain the gold standard for quantifying evoked responses.

Reversal of Neuromuscular Blockade

Nondepolarizing Blockade

As previously reviewed, acetylcholinesterase is present in high concentrations at the neuromuscular junction. It hydrolyzes ACh into choline and acetic acid, terminating the effects of ACh. The effects of nondepolarizing muscle relaxants are antagonized by administering an anticholinesterase (also known as an acetylcholinesterase inhibitor). This class of drugs inhibits the enzyme acetylcholinesterase, increasing the concentration of ACh molecules at the neuromuscular junction. Since nondepolarizing muscle relaxants and ACh compete for the same postsynaptic binding sites, the ACh increase can tip the balance of competition in favor of ACh, and neuromuscular transmission is restored.

The anticholinesterase drugs used to antagonize neuromuscular blockade include edrophonium, neostigmine, and pyridostigmine. They differ in how they inhibit acetylcholinesterase activity. Edrophonium produces a reversible inhibition by electrostatic attachment to the anionic site and by hydrogen bonding at the esteratic site on acetylcholinesterase. The action of edrophonium is relatively brief because a covalent bond is not formed and ACh can easily compete with edrophonium for access to the enzyme. Neostigmine and pyridostigmine inhibit acetylcholinesterase by forming a carbamyl-ester complex at the esteratic site of acetylcholinesterase. This bond lasts longer when compared with the bond of the enzyme with ACh, thereby preventing acetylcholinesterase from accessing ACh.

The reversal agents vary in their onset of action. In order from the shortest to the longest onset is edrophonium < neostigmine < pyridostigmine. In human patients, neostigmine is 4.4 times more potent than pyridostigmine and 5.7 times more potent than edrophonium for reversal of nondepolarizing neuromuscular blockade.[144] The duration of action is similar for both neostigmine and edrophonium, whereas that of pyridostigmine is approximately 40% longer.[144,145] In cats, neostigmine is 12 times more potent than edrophonium.[146]

Antiacetylcholinesterase agents are primarily metabolized by the liver, with hepatic biotransformation eliminating 50% of a neostigmine dose, 30% of an edrophonium dose, and 25% of a pyridostigmine dose. Renal excretion eliminates the remainder of the drug. Patients with renal failure will have prolonged elimination of an anticholinesterase drug.

The ACh accumulation following the administration of an anticholinesterase drug is not specific to the neuromuscular junction. While nicotinic effects occur at the neuromuscular junction and autonomic ganglia, muscarinic cholinergic effects occur because of inhibition of acetylcholinesterase at the sinus node, smooth muscle, and glands. Clinical effects of increased ACh concentrations at these sites include bradycardia, sinus arrest, bronchospasm, miosis, intestinal hyperperistalsis, and salivation. For this reason, it is advised that an anticholinergic drug, either atropine or glycopyrrolate, be administered immediately prior to re-

versal of neuromuscular blockade with an anticholinesterase. When choosing between atropine and glycopyrrolate, one must consider that atropine has a faster onset of action, which is more likely to cause an initial tachycardia, and will cross the blood-brain and blood-placental barriers. Compared with neostigmine and pyridostigmine, the muscarinic effects of edrophonium are mild, so it may be chosen for reversal when one wants to avoid the use of an anticholinergic. For example, edrophonium is frequently chosen in equine patients because anticholinergic drug administration has been associated with the development of ileus and colic.

Depolarizing Blockade

Recovery from succinylcholine (phase I block) is rapid and spontaneous because of succinylcholine hydrolysis by plasma cholinesterases. Recovery may be delayed in patients with decreases in plasma cholinesterase levels or activity. The administration of an anticholinesterase would actually prolong the depolarizing block.[147] On the other hand, a phase II block from succinylcholine can be antagonized similarly to the nondepolarizing muscle relaxants, emphasizing the need for determining the type (phase I or phase II) of block present when using succinylcholine (Table 15.2).[148,149]

Centrally Acting Muscle Relaxants

Guaifenesin is used routinely as a muscle relaxant in large animal species. Its mechanism of action is to disrupt nerve impulse transmission at the level of the internuncial neurons of the spinal cord, brain stem, and subcortical areas of the brain. At therapeutic doses, skeletal muscle relaxes, but there is little effect on the respiratory muscles or diaphragm. Guaifenesin does not provide analgesia or produce unconsciousness. Therefore, it should not be used alone for any painful surgical or diagnostic procedure. No antagonist is available to reverse the muscle relaxant effects of guaifenesin.

Guaifenesin is commercially available as either a powder, which is reconstituted to the desired concentration with sterile water, or as a ready-made solution. Concentrations of 5%, 10%, and 15% have been used, with a 5% solution in 5% dextrose being the most common. Guaifenesin administered intravenously in high concentrations (>10%) can cause hemolysis, hemoglobinuria, and venous thrombosis.[150] Tissue can be damaged if guaifenesin is inadvertently administered perivascularly.[150]

The cardiopulmonary effects of guaifenesin, alone or in combination with xylazine, ketamine, or thiobarbiturates, have been studied in horses. When guaifenesin is given alone, heart rate, respiratory rate, right atrial pressure, pulmonary arterial pressure, and cardiac output are unchanged. Systolic, diastolic, and mean arterial pressures are decreased. Xylazine (1.1 mg/kg IV), given prior to guaifenesin administration, reduced the dose necessary to achieve lateral recumbency (88 ± 10 mg/kg) compared with guaifenesin alone (134 ± 34 mg/kg). The addition of xylazine typically decreases heart rate, respiratory rate, cardiac output, and arterial oxygen partial pressure (PaO_2). Central venous pressure increases, whereas systolic, diastolic, and mean arterial blood pressures commonly decrease.[151,152]

Guaifenesin can be combined with thiopental for both induction and maintenance of anesthesia in horses. Following premedication with either xylazine or acepromazine, a combination of guaifenesin and thiopental (2 to 3 g of thiopental in 1 L of 5% guaifenesin) is given for induction or, alternatively, guaifenesin is given until the horse is wobbly and buckling at the knees, and then a bolus of thiopental (4 mg/kg) is administered. Short periods of anesthesia (<1 h) can be maintained by a continuous infusion of the guaifenesin-thiopental combination.

A significant amount of guaifenesin crosses the placental barrier in pregnant mares.[152] Stallions may have up to 1.5 times longer recovery time in male horses is attributed to slower drug elimination from the plasma.[153]

Guaifenesin has also been combined with thiobarbiturates or ketamine for use in cattle, small ruminants, and swine.[154,155] Although guaifenesin has been used in dogs, the large volume requirement makes it impractical for routine use in this species.[156] However, when combined with a thiobarbiturate or ketamine-xylazine, guaifenesin has proven an effective component when immobilizing dogs.[157]

Peripherally Acting Muscle Relaxants

Dantrolene is a hydantoin derivative that interferes with excitation-contraction coupling, thus relaxing skeletal muscle through a decrease in the amount of calcium released from the sarcoplasmic reticulum. Therapeutic doses do not adversely affect cardiac or smooth muscle and do not depress respiration.[158] Dantrolene is the drug of choice for the treatment of malignant hyperthermia. In swine, the recommended dose is 1 to 3 mg/kg IV when treating a malignant hyperthermia crisis and 5 mg/kg orally for prophylaxis.[159] Dantrolene is supplied in 20-mg vials in powder form with 3 g of mannitol to improve solubility. It is reconstituted using 60 mL of sterile water to achieve a concentration of 0.33 mg/mL. The oral preparation comes in 50-mg capsules.

The prophylactic use of dantrolene in animal patients prone to malignant hyperthermia is no longer routinely recommended. Pretreatment with dantrolene prior to anesthesia does not guarantee effective blood levels and, in equine patients, may produce unwanted skeletal muscle weakness during the recovery period. In susceptible patients, an anesthetic regimen using nontriggering anesthetics should be used, and dantrolene should be immediately available. However, the intravenous preparation of dantrolene may be cost prohibitive and not economically justifiable for many veterinary clinics to keep in stock. Most human hospital pharmacies have the intravenous formulation and may sell the needed amount to the veterinary clinic when required. Compounding the oral preparation for intravenous use has been described. The process is complex and time consuming, but dantrolene powder can be stored for rapid reconstitution during a malignant hyperthermia crisis.[160,161]

Metabolism of dantrolene is via the liver through oxidative and reductive pathways. Metabolites and the unchanged drug are excreted in the urine. Dantrolene can cause muscle weakness, nausea, and diarrhea. Fatal hepatitis has occurred in human patients

after chronic treatment with dantrolene.[162] Severe myocardial depression has been reported when dantrolene is administered concurrently with verapamil or other calcium channel blockers.[163,164] Synergism, resulting in a delayed recovery of neuromuscular function, has been observed with dantrolene and vecuronium coadministration.[165]

References

1. Griffith HR, Johnson GE. The use of curare in general anaesthesia. Anesthesiology 1942;3:418–420.

2. Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinylcholine: A new approach to muscular relaxation in anesthesiology. N Engl J Med 1952;247:596–600.

3. Pickett D. Curare in canine surgery. J Am Vet Med Assoc 1951; 119:346–353.

4. Miller RM. Psychological effects of succinylcholine chloride immobilization in the horse. Vet Med Small Anim Clin 1966;61:941–943.

5. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–943.

6. Edwards C. The effects of innervation on the properties of acetylcholine receptors in muscle. Neuroscience 1979;4:565–584.

7. Steinbach JH. Neuromuscular junctions and alpha-bungarotoxin-binding sites in denervated and contralateral cat skeletal muscles. J Physiol 1981;313:513–528.

8. Fambrough DM. Control of acetylcholine receptors in skeletal muscle. Physiol Rev 1979;59:165–227.

9. Stya M, Axelrod D. Mobility of extrajunctional acetylcholine receptors on denervated adult muscle fibers. J Neurosci 1984;4: 70–74.

10. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: A review. Anesthesiology 1984;61:173–187.

11. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.

12. Hirokawa N, Heuser JE. Internal and external differentiations of the postsynaptic membrane at the neuromuscular junction. J Neurocytol 1982;11:487–510.

13. Changeux JP, Bon F, Cartaud J, et al. Allosteric properties of the acetylcholine receptor protein from Torpedo marmorata. Cold Spring Harb Symp Quant Biol 1983;48(Pt 1):35–52.

14. Stroud RM, Finer-Moore J. Acetylcholine receptor structure, function, and evolution. Annu Rev Cell Biol 1982;1:317–351.

15. Fairclough RH, Finer-Moore J, Love RA, Kristofferson D, Desmeules PJ, Stroud RM. Subunit organization and structure of an acetylcholine receptor. Cold Spring Harb Symp Quant Biol 1983; 48(Pt 1):9–20.

16. Guy HR. A structural model of the acetylcholine receptor channel based on partition energy and helix packing calculations. Biophys J 1984;45:249–261.

17. Neubig RR, Boyd ND, Cohen JB. Conformations of Torpedo acetylcholine receptor associated with ion transport and desensitization. Biochemistry 1982;21:3460–3467.

18. Sheridan RE, Lester HA. Functional stoichiometry at the nicotinic receptor. J Gen Physiol 1982;80:499–515.

19. Brown RD, Taylor P. The influence of antibiotics on agonist occupation and functional states of the nicotinic acetylcholine receptor. Mol Pharmacol 1983;23:8–16.

20. Madsen BW, Albuquerque EX. The narcotic antagonist naltrexone has a biphasic effect on the nicotinic acetylcholine receptor. FEBS Lett 1985;182:20–24.

21. Albuquerque EX, Akaike A, Shaw DP, Rickett DL. The interaction of anticholinesterase agents with the acetylcholine receptor-ionic channel complex. Fundam Appl Toxicol 1984;4(2 Pt 2):S27–S33.

22. Cohen JB, Boyd ND, Shera NS. Interactions of anesthetics with nicotinic postsynaptic membranes isolated from Torpedo electric tissue. Prog Anesthesiol 1980;2:165–174.

23. Dreyer F. Acetylcholine receptor. Br J Anaesth 1982;54:115–130.

24. Lambert JJ, Durant NN, Henderson EG. Drug-induced modification of ionic conductance at the neuromuscular junction. Annu Rev Pharmacol Toxicol 1983;23:505–539.

25. Colquhoun D, Sheridan RE. The modes of action of gallamine. Proc R Soc Lond [B] 1981;211:181–203.

26. Ogden DC, Colquhoun D. Ion channel block by acetylcholine, carbachol, and suberyldicholine at the frog neuromuscular junction. Proc R Soc Lond [B] 1985;225:329–355.

27. Shanks CA. Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. Anesthesiology 1986;64:72–86.

28. Upton RA, Nguyen TL, Miller RD, Castagnoli N Jr. Renal and biliary elimination of vecuronium (ORG NC 45) and pancuronium in rats. Anesth Analg 1982:61:313–316.

29. Birch JH, Foldes FF, Rendell-Baker L. Causes and prevention of prolonged apnea with succinylcholine. Curr Res Anesth Analg 1956;35:609–633.

30. Pantuck EJ. Ecothiopate iodide eye drops and prolonged response to suxamethonium. Br J Anaesth 1966;38:406–407.

31. Kopman AF, Strachovsky G, Lichtenstein L. Prolonged response to succinylcholine following physostigmine. Anesthesiology 1978; 49:142–143.

32. Bentz EW, Stoelting RK. Prolonged response to succinylcholine following pancuronium reversal with pyridostigmine. Anesthesiology 1976;44:258–260.

33. Short CE, Cuneio J, Cupp D. Organophosphate-induced complications during anesthetic management in the horse. J Am Vet Med Assoc 1971;159:1319–1327.

34. Reynolds WT. Use of suxamethonium in cats fitted with dichlorvos flea collars. Aust Vet J 1985;62:106–107.

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

36. 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.

37. Playfor SD, Thomas DA, Choonara I. The effect of induced hypothermia on the duration of action of atracurium when given by infusion to critically ill children. Paediatr Anaesth 2000;10:83–88.

38. Scott RP, Savarese JJ, Basta SJ, et al. Clinical pharmacology of atracurium given in high dose. Br J Anaesth 1986;58:834–838.

39. Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of mivacurium chloride administered to patients during oxygen-sufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesth Analg 1989;68:333–339.

40. Wastila WB, Maehr RB, Turner GL, Hill DA, Savarese JJ. Comparative pharmacology of cisatracurium (51W89), atracurium, and five isomers in cats. Anesthesiology 1996;85:169–177.

41. Sparr HJ, Beaufort TM, Fuchs-Buder T. Newer neuromuscular blocking agents: How do they compare with established agents? Drugs 2001:61:919–942.

42. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (ORG