14 Muscle Relaxants and Neuromuscular Blockade

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Chapter contents

History of muscle relaxants

Muscle relaxants are a group of 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 the fact that this class of drugs produce their effects by action at the neuromuscular junction. The more general term muscle relaxant refers to any drug having relaxant properties and would include centrally acting agents such as benzodiazepines, α_2-adrenergic receptor 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, neurologic, or cardiothoracic surgery. While used frequently in human anesthesia and in some veterinary specialty practices 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'; that is, they provide unconsciousness, analgesia, and muscle relaxation. All three of these properties are required to permit 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 while substantially deeper planes are required to provide analgesia and muscle relaxation. Indeed, these last two properties are provided by potent inhalant anesthetics only by virtue of general CNS depression. 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 the adverse effect of reduced cardiovascular performance. In young, healthy animals having good cardiovascular reserve this may be tolerated, but in patients with poor cardiovascular function, significant morbidity and mortality may result.

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Rather than using an inhalant anesthetic to provide all three components of the triad, a safer, smoother anesthetic technique, particularly in patients with cardiovascular compromise, may be one that uses low concentrations of inhalant anesthetic to provide unconsciousness, opioids to provide analgesia, and a NMBA to provide muscle relaxation. Techniques such as this may be termed *balanced anesthesia* in that a mixture of agents at smaller doses is chosen based upon what they do reasonably well. Balanced anesthesia techniques are frequently chosen because they provide optimal conditions for both the surgeon and the patient.

The introduction of NMBAs into anesthesiology is a relatively recent event in medical practice, occurring in 1942. South Americans had for centuries been using a poison, derived from the tropical plant *Chondodendron tomentosum,* on the heads of their hunting arrows which had the property of causing paralysis and death to quarry. Such a poison was an obvious advantage in that animals suffering even a minor wound would succumb and be harvested by the hunter. The existence of this poison, known as curare, was recognized outside South America, but what possible use would an arrow poison have in medicine? The link was made when the explorer Richard Gill returned from the jungles of Ecuador 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 who purified the raw mixture 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 as 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 which 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 having a benzylisoquinolinium structure, isolated from raw curare, was safe and useful for producing abdominal muscle relaxation during general anesthesia began to emerge and use of the drug spread to 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 [1]. Reports of veterinary use of NMBAs in dogs began to appear also in the early 1950s [2] and administration of succinylcholine to horses was described in the 1960s [3].

Both d-tubocurarine [4] and succinylcholine have a number of undesirable cardiovascular effects. Both agents can affect autonomic ganglia and cardiac muscarinic receptors, and cause release of histamine. Although succinlycholine has the advantage of rapid onset and offset compared with d-tubocurarine, additional disadvantages of possible hyperkalemia, arrhythmias, postanesthetic myalgia, and the changing nature of its block dictated that other NMBAs would be developed.

Synthetic relaxants developed during the ensuing years included gallamine, decamethonium, alcuronium and finally the steroid-based pancuronium. Most are now only of historical interest, although alcuronium is still frequently used in many parts of the world and the steroid molecule of pancuronium serves as a parent molecule of several contemporary NMBAs. Atracurium and vecuronium, introduced in the 1980s, have the advantage of minimal to no cardiovascular effects, minimal histamine release, and a controllable and predictable duration of action. Both are widely used in human anesthesia practice. Recently developed NMBAs include doxacurium, pipecuronium, and cisatracurium. All of these drugs represent continuing efforts to develop neuromuscular blockade with fewer cardiovascular and hemodynamic side-effects.

A prime indication for the use of NMBAs in human practice is tracheal intubation during induction of anesthesia. Despite its undesirable effects, succinylcholine remains the gold standard for facilitating tracheal intubation in humans primarily due to rapid onset and short duration of action. A search for a non-depolarizing alternative to succinylcholine has resulted in the development of mivacurium, an analogue of atracurium, and rocuronium, a steroidal drug derived from pancuronium. Despite improvements in speed of onset, neither mivacurium nor rocuronicum is able to facilitate human tracheal intubation as rapidly as succinylcholine. The latest NMBA to be developed, gantacurium, has an ultra-short duration of action and an onset time approaching that of succinylcholine. Structurally distinct from any previously released NMBA, gantacurium is currently undergoing human clinical trials and may eventually replace succinylcholine as an adjunct to human tracheal intubation.

Physiology of the neuromuscular junction

All NMBAs exert their effects at the neuromuscular junction or motor endplate. The neuromuscular junction 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 pre- 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 receptor is found on the motor endplates of normal adult animals and is responsible for binding with the released ACh and effecting a muscle contraction. Junctional receptors are therefore responsible for the relaxant effect seen when a NMBA is administered. The extrajunctional receptors are not normally present in the muscles of typical adults but they have importance because they are synthesized by muscles that are receiving a less than normal degree of motor nerve stimulation [7]. Thus they are produced by muscles following a spinal cord or peripheral nerve injury or after a period of disuse as when a limb is casted. They are also present in neonates. The location of extrajunctional receptors is not restricted to the motor endplate and they may be located over the entire muscle cell surface [8,9].

Extrajunctional receptors appear to be more sensitive to depolarizing NMBAa such as succinylcholine and less sensitive to non-depolarizing NMBAs such as atracurium [10]. If the degree of neural deficit is severe, extrajunctional receptors may be numerous and widely distributed over the muscle membrane. Such patients may have very different responses to the actions of depolarizing NMBA and thus profound release of intracellular K^+ with concomitant adverse cardiac effects may result if succinylcholine is administered to these patients [11].

The prejunctional nerve ending synthesizes and stores a quantity of ACh in synaptic vesicles and this ACh acts as a neurotransmitter, thus coupling the nerve impulse with a resultant muscular contraction. During the course of normal neuromuscular transmission, an action potential arrives at the prejunctional motor nerve ending causing depolarization of the nerve terminal which results in release of ACh. The release of packets or quanta of ACh in response to membrane depolarization is a Ca^{++}-dependent process. The depolarization of the nerve membrane results in activation of adenylate cyclase which converts adenosine triphosphate to cyclic adenosine monophosphate. The resultant conversion results in Ca^{++} entry into the nerve terminal and subsequent release of ACh into the synaptic cleft. As mentioned previously, ACh is the neurotransmitter that effectively couples the nerve action potential into a muscular contraction. This coupling is accomplished by interaction of ACh with the postjunctional nicotinic receptor.

The interaction of ACh with the nicotinic receptor is associated with the development of an endplate potential (a muscle cell action potential) and ultimately muscular contraction. The ACh released from the prejunctional nerve cell is short-lived in that it is rapidly hydrolyzed into choline and acetate via the enzyme acetylcholinesterase. Thus the postjunctional muscle cell is depolarized by the endplate potential created by the binding of ACh to the receptor and then is repolarized as the ACh is removed from the receptor and is hydrolyzed.

The postjunctional receptors are concentrated on the endplate immediately opposite the ACh release sites on the prejunctional membrane [12]. Electron microscopy of these receptors shows them to have a central pit surrounded by a raised circular area [13,14] and thus they look similar to a spool of thread that is viewed end on. The raised circular area is the mouth of a cylinder of a receptor protein that protrudes through the membrane and contains the binding sites where ACh and other ligands attach. The pit is the opening of an ion channel that is contained within the cylinder and runs throughout its length. The receptor protein is composed of five subunits composed of two α, and one each of β, γ, and δ subunits. They are arranged into a cylinder having a potential space, the ion channel, contained within [15]. The opening of the channel is controlled by the ACh binding sites present in the two α subunits. When molecules of ACh are bound to the binding sites on each of the two α subunits, the protein rotates into a new configuration and in so doing opens the ion channel and permits ion flow [16]. The channel permits the flow of small cations but not large cations or anions. Thus during normal neuromuscular transmission, binding of two molecules of ACh to the α subunits opens the channel and permits Na^+ and Ca^{++} to flow in and K^+ to flow out of the channel. Electrical current flow thus occurs with resultant depolarization of the postjunctional membrane [17]. As the ACh molecules leave the receptor and are hydrolyzed by acetylcholinesterase, the ion channel closes, current flow stops and repolarization of the membrane occurs.

Binding of ligands to the receptor is a competitive process. Whichever suitable ligand is present in highest concentration in the vicinity of the receptor will win the competition and affect the outcome. Since two molecules of ACh are required to bind to each of the α subunits on the receptor [18], antagonists have a distinct advantage in that they need only bind to one of the subunits to prevent normal neuromuscular transmission. Contraction of the muscle does not occur in response to motor nerve depolarization and paralysis results.

The interaction of ACh and NMBA at the postjunctional receptors is a dynamic process of binding and release and, coupled with the sheer number of receptors present (10–20,000/μm^2), the success or failure of neuromuscular transmission in the presence of a NMBA is determined by the concentration of the NMBA versus the concentration of ACh. A high percentage of receptors binding ACh favors muscular contraction while a high percentage of receptors binding NMBA favors paralysis. This suggests a method for reversing paralysis induced by a NMBA. Increasing the concentration of ACh compared with the concentration of NMBA will increase the probability that ACh will win the competition for the receptor and restore normal neuromuscular transmission. Clinically this is accomplished by administration of acetylcholinesterase inhibitors. When an anticholinesterase drug such as neostigmine is administered, the available ACh is not degraded immediately, but persists within the synapse and is able to repeatedly interact with receptors. This tips the competitive balance in favor of ACh; more receptors participate in current flow and global muscle strength increases. Such interaction is also seen as the activity of a NMBA wanes due to elimination of the drug.

Pharmacology

Ligand–receptor interactions

The classic interaction of a NMBA such as d-tubocurarine or atracurium and the cholinergic receptor involves a competitive binding of the drug to the receptor, thus inhibiting the coupling of nerve action potential transmission with muscular contraction. There are at least two other less understood mechanisms, desensitization and channel blockade, where drugs may interact with the ACh receptors and disrupt neuromuscular transmission. Earlier it was stated that the cholinergic receptor is in an inactive state with its potential ion channel collapsed when two molecules of ACh are not attached to the α subunits' binding sites. Binding of ACh to each of the two α subunits of the receptor causes conformational change and allows the ion channel to open to the active state, depolarization occurs and muscle contraction ensues. A third possibility exists and is called the desensitized state. Receptors existing in the desensitized state bind ACh to the α subunits but conformational change and channel opening do not occur, so the receptor is said to be desensitized. 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 since it is known clinically that low doses of NMBA achieve an acceptable degree of relaxation when the patient is anesthetized with a volatile anesthetic. A large number of drugs may cause or promote desensitization such as succinylcholine, thiopental, Ca^{++} channel blockers, local anesthetics, phenothiazines, cyclohexamines, inhalant anesthetics, and some antibiotics [19–22]. Channel blockade can occur when the cholinergic receptor binds an agonist to each of the α subunits, the ion channel opens, and a molecule becomes stuck within the channel. This is possible because the mouth of the ion channel is much wider than the transmembrane spanning region, thus permitting molecules to enter the channel but not to cross it. Entrapped molecules act like plugs in a funnel and interfere with the normal passage of ions in response to the binding of ACh. Channel blockade therefore 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 make the block more intense since 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 cause blockage of the neuromuscular receptor channels may provide a partial explanation as to why administration of an anticholinesterase drug in an effort to antagonize a profound neuromuscular blockade may actually intensify rather than lessen the paralysis [25,26].

Depolarizing and non-depolarizing drugs

Earlier a distinction was made between two main categories of NMBA: non-depolarizing represented by drugs such as d-tubocurarine and atracurium and depolarizing represented by succinylcholine. Both groups have affinity for the ACh receptor and therefore act as competitors of ACh. However, their intrinsic activity once bound to the receptor site is very different. Non-depolarizing drugs bind to the receptor but do not activate it. That is, the ion channel is not opened in response to their binding. These non-depolarizing drugs may be thought of as competing for the receptor, thus preventing the endogenous ligand, ACh, from binding and causing current flow. The onset of action of these drugs is characterized by a progressive weakening of muscle contraction and ultimately flaccid paralysis.

Depolarizing drugs also bind to the receptor and, similar to the actions of ACh, the receptor is stimulated, undergoes conformational change and results in current flow and depolarization of the postjunctional membrane. Unlike ACh, however, succinylcholine and other depolarizing NMBAs are not susceptible to breakdown by acetylcholinesterase and thus the ion channel remains open and repolarization does not occur. The persistent state of depolarization associated with administration of a depolarizing NMBA results in inexcitability of the motor endplate and, as with a non-depolarizing NMBA, a flaccid paralysis.

In addition to the differing mechanism of action of the depolarizing drugs, several other differences are clinically apparent when comparing depolarizing and non-depolarizing NMBA. The initial depolarization of the motor endplate associated with succinylcholine binding to and activating the postjunctional ACh receptors leads to the initial, unco-ordinated contractions seen clinically as fasciculations. Large doses of succinylcholine, repeated administration, or administration of the drug as an infusion result in a change in the character of the block from the classic depolarizing action described above to a block known as Phase II block which resembles that of non-depolarizing 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 results in receptor desensitization, channel blockade or a combination of both. Both receptor desensitization and channel blockade have properties that would mimic those of the non-depolarizing NMBAs and thus would change the nature of the succinylcholine-induced block.

Individual neuromuscular blocking drugs

The NMBAs are quaternary ammonium compounds designed to mimic the quaternary nitrogen atom of ACh. They bind to the cholinergic receptors at the motor endplate as well as to cholinergic 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 metabolism. The water-soluble nature of these compounds dictates that their pharmacokinetics differ markedly from most anesthetic drugs clinicians are familiar with such as thiopental, propofol, and ketamine. A hallmark of these lipid-soluble anesthetic agents is their rapid onset of action and their rapid termination of effect after IV administration (see Table 14.1). The lipid solubility of these agents dictates that the induction drugs will gain entrance to the site of action in the brain by rapidly crossing cellular membranes such as the blood–brain barrier. Termination of anesthetic effect is achieved by rapid metabolism and by redistribution to the skeletal muscles and ultimately the adipose tissue.

Table 14.1 Approximate doses and duration of action of muscle relaxants given intravenously to dogs.

Muscle relaxant	Approximate dose (μg/kg)	Approximate duration (min)	Twitch recovery signifying end point of duration (% of baseline twitch)	References
Atracurium	200–400	17–28.9	50%	38
Doxacurium	3.5	108	75%	56
Gantacurium	60	3–6	95%	63
Mivacurium	10	35.1	100%	58
Pancuronium	22–100	31–108	50–100%	68
Pipecuronium	3.7–50	16–80.7	50%	55
Rocuronium	122	6.7	90%	50, 51
Succinylcholine	300–400	22–29	10–50%	33
d-Tubocurarine	130	100	50%	4
Vecuronium	14–200	15–42	50%	4, 47

Note: Twitch recovery applies to those experimental studies where evoked muscle contractions following nerve stimulation were measured.

The poor lipid solubility of the NMBAs is primarily due to the positive charges present at the quaternary ammonium moieties of the molecules [27]. The low lipid solubility exhibited by the NMBAs dictates the pharmacokinetics and pharmacodynamics of these drugs. Transfer across membrane structures including the placenta and blood–brain barrier is poor, resulting in decreased distribution compared with the lipid-soluble anesthetic drugs. Hepatic metabolism and redistribution to sites other than the skeletal muscles are usually not major mechanisms whereby the action of the NMBA is terminated. Exceptions include vecuronium where biliary excretion is important in the elimination of vecuronium from the body [28]. Due to their water solubility, most NMBAs are easily excreted by glomerular filtration into the urine and are generally not reabsorbed by the renal tubules. The water-soluble nature of these drugs may also contribute to the observation that neonates require higher relative doses of NMBA since neonates have a higher percentage of body water, and thus a higher volume for water-soluble drugs to distribute into, than do adults. Some reported doses for NMBAs in dogs, cats, and horses are included in Table 14.2.

Succinylcholine

Succinylcholine is currently the only depolarizing NMBA used clinically in veterinary medicine. Structurally, the succinylcholine molecule is two acetylcholine molecules joined together, or diacetylcholine. The drug is so rapidly hydrolyzed in plasma by the enzyme pseudocholinesterase (plasma cholinesterase) that only a small fraction of the original 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

Table 14.2 Intravenous doses of selected neuromuscular junction blocking agents used in the dog, cat, and horse.

Drug (mg/kg)	Dog	Cat	Horse
Succinylcholine	0.3–0.4	0.2	0.12–0.15
Pancuronium	0.07–0.1	0.06–0.1	0.12
Atracurium	0.1–0.2	0.1–0.25	0.07–0.15
Vecuronium	0.1	0.025–0.1	0.1
Pipecuronium	0.05	0.003	
Cisatracurium	0.075–0.3	0.05–0.3	
Mivacurium	0.01–0.05	0.08	
Gantacurium (GW280430A)	0.06	0.06	
Rocuronium	0.1–0.6	0.1–0.6	0.3–0.6
Doxacurium	0.002–0.005		

Equipotent doses for neuromuscular junction blocking agents are often reported at the ED_{95}. Clinical paralysis may require more or less drug depending on the concurrent anesthetic agents used, the speed of onset required, the duration of block desired, and the area of the body where muscle relaxation is needed. Repeated doses are usually administered at approximately half of the original dose required to cause paralysis.

termination of succinylcholine-induced paralysis is due to diffusion of the drug away from the neuromuscular junction and into the extracellular fluid. Paradoxically, the rapid degradation of succinylcholine in the plasma is 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 fear of an increased duration of effect. The higher the initial dose of a NMBA, the more rapid the onset of paralysis but also, in the case of all currently available NMBAs except succinylcholine and perhaps gantacurium, a significant increase in the duration of action results. Because of the rapid onset of effect and short duration of action, succinylcholine is often referred to as the relaxant of choice to facilitate human endotracheal intubation. Use of NMBAs to facilitate endotracheal tube placement is not common in veterinary practice since, with the arguable exception of the cat and pig, laryngeal activity is rarely an impediment to tracheal intubation.

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]. A reduction in plasma cholinesterase activity may be expected to result in a prolonged duration of action of succinylcholine [33]. Administration of organophosphate insecticides such as diclorovos and trichlorfon to horses has been shown to reduce pseudocholinesterase activity and prolong the duration of succinylcholine-induced neuromuscular blockade [34]. Conversely, cats wearing a dichlorvos flea collar had no increased duration of effect from succinylcholine [35].

Pancuronium

Pancuronium was the first in a series of non-depolarizing NMBAs having a steroid molecule base structure. The drug has a dose-dependent onset of approximately 5 min and a duration of action ranging from 40 to 60 min in dogs [36]. Repeated doses have a cumulative effect so administration via infusion is not common. A large fraction of the drug is excreted by the kidney, the remainder is metabolized by the liver. As may be expected, the duration of action is increased in patients presenting with renal insufficiency. In addition to having affinity for the cholinergic receptors at the neuromuscular junction, pancuronium also appears to block cardiac muscarinic receptors, resulting in an increase in heart rate. This effect appears to vary among species and usually is not a clinical concern. The muscaranic blocking effect and associated tachycardia appear to be due to the presence of a second positive charge attached to the steroid ring. Removal of a single methyl group and thus of the positive charge creates vecuronium, a NMBA essentially devoid of cardiovascular effects.

Atracurium

Atracurium is a short-acting non-depolarizing NMBA having a benzylisoquinoline structure similar to that of d-tubocurarine. The drug has a dose-dependent onset of approximately 5 minu and dependent duration of action of approximately 30 min in dogs [37]. Repeated doses do not tend to be cumulative so longer term maintenance of neuromuscular blockade via infusion is viable. Atracurium is unique in that almost half of the drug is degraded by Hofmann elimination and non-specific ester hydrolysis. The remaining fraction of the drug is degraded by as yet undefined routes although evidence exists that duration of action is not prolonged in humans with hepatic or renal failure [38,39]. Hepatic metabolism and renal excretion are thus not strictly necessary for termination of the paralytic effect and consequently atracurium may be administered to patients with hepatic or renal insufficiency without an increase in the duration of action. The drug should be refrigerated and is supplied at a pH of 3.25–3.65 to slow degradation. Hofmann elimination is not a biologic process and does not require enzymatic activity. When injected IV at physiologic pH and temperature, atracurium spontaneously decomposes into laudanosine and a quaternary monoacrylate. Laudanosine is a known CNS stimulant and has the potential to induce seizures. Unlike atracurium, laudanosine is dependent upon hepatic clearance so laudanosine plasma concentrations may be elevated in patients with hepatic insufficiency. Despite the theoretical concerns, laudanosine-induced CNS stimulation and resultant seizures are unlikely in clinical patients unless the drug is used for prolonged periods of time as might occur in intensive care settings.

Since Hofmann elimination is a pH- and temperature-dependent process, hypothermia will increase the duration of atracurium neuromuscular blockade and will decrease the infusion rate necessary to maintain neuromuscular blockade [40]. Ester hydrolysis of atracurium is accomplished by several plasma esterases not related to plasma cholinesterase. In contrast to the depolarizing relaxant succinylcholine, duration of action is not prolonged in the presence of cholinesterase inhibitors.

Many NMBAs with the benzylisoquinolone structure are associated with histamine release and a varying degree of resultant hypotension. d-Tubocurarine, the prototypical benzylisoquinolone NMBA, is among the most potent histamine-releasing NMBAs but newer drugs having the benzylisoquinolone structure such as atracurium and mivacurium require several times the ED_{95} dose required for neuromuscular blockade before appreciable amounts of histamine are released [41,42]. Although atracurium has the potential to result in histamine release, problems such as hypotension and tachycardia are not usually observed in clinical cases.

Cisatracurium

Atracurium is a racemic mixture of ten optical isomers. The 1R-*cis*, 1R′-*cis* isomer, or cisatracurium, comprises approximately 15% of racemic atracurium and has approximately four times the potency and a reduced potential for histamine release. Indeed, in a study of cats, plasma histamine concentrations were unchanged when up to 60 times the ED_{95} of cisatracurium was administered [43]. Cisatracurium has a similar onset and duration of action as

atracurium. Hofmann elimination is responsible for greater than half of the administered dose of cisatracurium but unlike atracurium, ester hydrolysis does not occur. As with atracurium, the Hofmann elimination process results in laudanosine production. Since cisatracurium is approximately four times as potent as atracurium, the administered dose is correspondingly less as is the resultant production of laudanosine [44].

Vecuronium

Introduced in the 1980s, vecuronium was one of the first NMBAs devoid of cardiovascular effects. The discovery that the vagolytic properties seen with administration of pancuronium were due to the presence of two positive charges within the steroid molecule led investigators to remove a single methyl group from the parent pancuronium molecule. Vecuronium, the resultant drug, does not induce tachycardia or promote histamine release [45]. Indeed, in dogs vecuronium does not alter arterial blood pressure [46]. This drug has a dose-dependent onset of action of approximately 5 min and an intermediate 30-min duration of action similar to that of atracurium. 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 thus it 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 microsomes and excreted in the bile while a significant fraction undergoes renal elimination [47]. In humans the duration of action of vecuronium is either slightly prolonged or unchanged in patients exhibiting renal insufficiency. In patients with hepatic failure the duration of action is prolonged only if increased doses are administered [48].

Rocuronium

Rocuronium 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 larger injected dose of rocuronium places a greater number of molecules near the neuromuscular junction, translating into a more rapid onset of neuromuscular blockade. Despite a more rapid onset compared with atracurium and vecuronium, rocuronium cannot provide optimal conditions for human tracheal intubation as quickly as succinylcholine. Duration of action in the dog is similar to that of vecuronium and atracurium [49,50]. Similar to vecuronium, rocuronium seems to be virtually without cardiovascular adverse effects and does not cause histamine release [51]. The primary route of elimination is via the hepatic system while a small fraction is eliminated via the kidney [42]. The neuromuscular blocking effects of rocuronium and vecuronium can be reversed by the administration of suggammadex, a chelating agent that preferentially binds to and physically removes the NMBA from the motor endplate [52–54].

Pipecuronium

Pipecuronium is another steroid relaxant derived from pancuronium. Manipulation of the steroid structure has resulted in a relaxant that has greatly reduced antimuscarinic effects so pipecuronium is free of tachycardic effects while retaining a long duration of action. It has resulted in hypotension in dogs [55]. Similar to pancuronium, pipecuronium is eliminated primarily via the renal route with a smaller fraction undergoing biliary excretion.

Doxacurium

Doxacurium is a very potent benzylisoquinilone NMBA having a long duration of action [56]. Similar to other benzylisoquinilone NMBAs such as atracurium, the drug does not have vagolytic properties or result in ganglion blockade. Similar to cisatracurium, administration of clinically useful doses of doxacurium does not result in appreciable histamine release. Doxacurium appears to be minimally metabolized and is excreted unchanged into the bile and urine.

Mivacurium

Mivacurium is a rapid-acting, short-duration NMBA marketed for use in human tracheal intubation. Similar to the related benzylisoquinolone drug atracurium, mivacurium has the potential to induce histamine release, particularly if high doses are administered as often occurs when a rapid onset of effect is desirable. Mivacurium is degraded by plasma pseudocholinesterase and metabolites do not have appreciable neuromuscular blocking activity. Typical administered doses in humans have a duration of action of approximately 25 min, thus being one-half to one-third shorter than atracurium. Mivacurium shows marked differences in potency and in duration of action among species, being much more potent in dogs than in humans. Indeed, in dogs one-third of the typical human dose is associated with a duration of blockade that is five times longer than in humans [57]. The differences in duration of action between species may in part reflect the circulating quantity of pseudocholinesterase present since normal plasma cholinesterase values for dogs are from 19% to 76% of human values [58]. In addition, it is possible that canine pseudocholinesterase enzyme has differing affinity for the three primary isomers of mivacurium found in the proprietary formulation [49]. Clinical observations in cats indicate that mivacurium has a much shorter duration of action in this species compared with dogs (RDK personal observation).

Gantacurium

Gantacurium is a rapid-acting, ultra-short duration non-depolarizing NMBA currently undergoing human clinical trials. It is structurally distinct from the traditional steroidal and benzylisoquinolinium compounds and is classified as an asymmetric mixed-onium cholorfumerate. Gantacurium is not stable in aqueous solution and, similar to vecuronium, the drug is provided as a lyophilized powder that is reconstituted prior to administration. The dose in humans required to produce a 95% block (ED_{95}) is 0.19 mg/kg [59]. Following IV bolus administration of 0.45–0.54 mg/kg (2.5–3× ED_{95}), optimal conditions for intubation were achieved in 90 s [57,60]. In addition to having a rapid onset in humans, gantacurium has a short duration of action of approximately 14 min for a dose of 0.4 mg/kg and, similar to succinylcholine, increasing the administered dose in an effort to increase onset does not markedly increase duration of action [61]. In dogs anesthetized with thiopental, nitrous oxide, and isoflurane, the ED_{95} was 0.06 mg/kg, onset time was 107 s, and duration of action was 5.2 min [62].

In humans, gantacurium has the potential to release histamine at doses exceeding 2.5× ED_{95}. The histamine release was accompanied by clinically significant decreases in blood pressure, increases in heart rate, and facial redness [57]. Conversely, clinically significant histamine release was not observed in dogs at IV bolus doses up to 25× ED_{95} [60].

Gantacurium has two degradation pathways that account for its predictably ultra-short duration of action. The first pathway is a pH-sensitive hydrolysis in plasma while the second involves the

binding of the non-essential amino acid cysteine to the gantacurium ring structure. Endogenous or exogenously administered cysteine replaces a chlorine atom and saturates the double bond of the fumerate moiety [63]. The gantacurium is thus rendered inactive and neuromuscular transmission resumes.

Non-neuromuscular effects of NMBAs

The NMBAs have a primary action at the nicotinic cholinergic receptors at the motor nerve plate but may also have effects at other cholinergic receptors throughout the body. Cholinergic receptors that may be affected by NMBA include cardiac muscarinic receptors and autonomic nervous system ganglia. Many of these undesirable effects involve either a blocking of the receptor or a mimicking of the action of ACh. In addition, many NMBAs promote the release of histamine and other vasoactive substances from mast cells. Still other undesirable effects may result from the initial muscle fasciculation associated with administration of depolarizing NMBAs such as succinylcholine.

Cardiovascular effects

Acetylcholine is the primary neurotransmitter at not only the nicotinic receptors at the motor endplate of skeletal muscles but at muscarinic receptors of the parasympathetic nervous system and at sympathetic ganglia as well. ACh is the primary neurotransmitter of pre- and postganglionic neurons within the parasympathetic nervous system while the sympathetic nervous system employs ACh as a preganglionic neurotransmitter. The ubiquitous presence of ACh and the structural similarities between ACh and the NMBAs provide opportunity for the NMBAs to have effects in addition to their paralytic actions. Stimulation or blocking of cardiac muscarinic receptors or of sympathetic ganglia may result in either increases or decreases in heart rate and the development of cardiac dysrhythmias. Succinylcholine can mimic the effect of ACh at cardiac muscarinic receptors, resulting in sinus bradycardia, junctional rhythms and even sinus arrest [64,65]. In contrast, by virtue of its ACh-like effects at sympathetic ganglia, administration of succinylcholine may result in increases in heart rate and blood pressure [66].

Non-depolarizing drugs, particularly the older agents, may also influence a patient's cardiovascular status. The rapid IV injection of a paralyzing dose of d-tubocurarine can result in a significant decrease in blood pressure. One possible mechanism is that the injected d-tubocurarine blocks the action of ACh at sympathetic ganglia, thus resulting in an effective decrease in sympathetic tone with resultant hypotension. Alternatively, histamine release associated with the rapid IV administration of d-tubocurarine is probably responsible for the majority of the hypotension seen since slow IV administration or prior administration of an antihistamine drug attenuates the decrease in blood pressure that is observed following administration [67]. Rapid IV administration of pancuronium is associated with an increase in heart rate and corresponding increases in arterial pressure and cardiac output [68,69]. This tachycardic effect has been shown to be due to blockade of cardiac muscarinic receptors and resultant decreased parasympathetic nervous system activity [70]. In addition there is evidence that pancuronium may stimulate the release of norepinephrine from sympathetic nerves [71].

The modest increase in heart rate is not always disadvantageous, particularly when drugs having bradycardic effects such as the opioids are co-administered to a patient receiving pancuronium. The ability of pancuronium to induce an increase in heart rate is inconsistent between species. In dogs, pancuronium increases heart rate, blood pressure, and cardiac output [55,56]. The heart rates of horses anesthetized with halothane and administered pancuronium did not change [72] but ponies had an increase in both heart rate and blood pressure [73]. Similar to the effect on horses, pancuronium did not change heart rate or blood pressure in anesthetized calves [74] but did result in increases in heart rate and blood pressure in pigs [75].

The newer, intermediate duration agents such as atracurium and vecuronium are virtually devoid of cardiovascular effects. Atracurium and mivacurium do have the potential to result in histamine release, but decreases in blood pressure are rarely seen clinically if the drugs are not administered as a rapid IV bolus. The newest drugs, pipecuronium, doxacurium, and rocuronium, were designed with cardiovascular stability in mind and are unlikely to be associated with profound changes in cardiovascular function.

Histamine release

The quaternary ammonium structure inherent in the NMBAs is responsible for the propensity of many of these compounds to result in histamine release following IV injection. Release of histamine in animals results in 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 NMBA but has been reported with steroid relaxants having low potency [76]. The relaxant d-tubocurarine is a potent releaser of histamine at doses required to produce neuromuscular block and thus histamine release, vasodilation and increased heart rate are commonly encountered [54]. For the newer NMBAs, the dose necessary to evoke clinically significant histamine release is much higher than the dose necessary to produce relaxation. For example, in humans approximately 2.5 times the ED_{95} dose of atracurium is required to cause clinically significant histamine release [77]. Pretreatment of patients with H_1 and H_2 receptor antagonists is effective in preventing the effects associated with histamine release [78]. In clinical patients, worries about histamine release with use of the newer NMBAs may be avoided simply by administering relaxants via slow IV injection and refraining from administration of greater than recommended doses.

Placental transfer

All clinically used NMBAs are large, hydrophilic polar molecules and as a consequence their transfer across cell membranes, including the placenta, is limited. At doses used clinically, placental transfer of relaxants is minimal and effects on the neonate are unlikely. There is current widespread use of NMBAs in human cesarean operations and atracurium and succinylcholine have been used clinically in small and large domestic animals without detection of effects on the neonate. Administration of NMBAs such as pancuronium, succinylcholine, gallamine, and d-tubocurarine to pregnant ferrets and cats does not impair muscle twitch strength in the neonate [79].

Central nervous system effects

Being large, polar, hydrophilic molecules, the NMBAs do not cross cell membranes readily. However, evidence exists that most of these drugs do gain entrance into the CSF and may be associated with resultant CNS effects. In one study, pancuronium was reported to reduce the MAC of halothane in humans [80]. However, a subsequent study found that pancuronium, atracurium or vecuronium had no effect on the MAC of halothane in humans [81]. Accidental administration of NMBA into the CSF has resulted in myotonia, autonomic effects, and seizures [82,83]. Laudanosine is a product of

atracurium degradation that easily crosses the blood–brain barrier in dogs [84] and, in large doses, may result in CNS stimulation. Clinically used dosages of atracurium, however, are extremely unlikely to result in the formation of sufficient quantity of laudanosine to cause CNS stimulation.

Protein binding

All non-depolarizing 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 addition, protein binding would be expected to reduce renal elimination since only free unbound drug is filtered at the glomerulus. In human studies of patients with 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 having normal plasma protein concentrations [85,86]. 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 states seems to remain unchanged.

Non-neuromuscular effects of succinylcholine

Several undesirable non-neuromuscular side-effects are associated with the administration of clinically useful doses of the non-depolarizing NMBA succinylcholine. These effects include hyperkalemia, increased intraocular, intracranial and intragastric pressure, and muscle soreness.

Hyperkalemia

Administration of succinylcholine is associated with a transient increase in serum potassium levels. Succinylcholine binds to and activates the nicotinic motor endplate receptors but unlike Ach, succinylcholine is not immediately degraded by acetylcholinesterase enzyme. Thus, a state of depolarization characterized by open ion channels persists. When the ion channels are open, potassium ions are able to exit from the muscle fiber into the extracellular fluid space. As a result, serum potassium concentrations rise transiently following administration of succinylcholine. However, in healthy patients this transient increase is without adverse effects provided that cardiovascular disease is not present and preadministration potassium levels are normal. In patients presenting with burns, severe muscle trauma, muscular denervation, nerve damage or neuromuscular disease, extrajunctional ACh receptors proliferate over the surface of the muscle fiber membrane. This increase in receptor density is associated with an increase in sensitivity to the depolarizing muscle relaxants and an increase in the amount of intracellular potassium released in response to administration of succinylcholine. The increase in ACh receptor density does not occur before about 2 days following the injury and seems to persist for 2–3 months [87]. Similar to the effect seen with burns or denervation injuries, prolonged immobilization of a limb is also associated with an increase in ACh receptor density. As with burn patients, increases in serum potassium levels may be expected if succinylcholine is administered to these patients.

Intraocular pressure

Administration of succinylcholine is associated with an increase in intraocular pressure. In humans, the intraocular pressure peaks at 2–4 min and remains increased for at least 6 min following administration [88]. The mechanism responsible for the increase in intraocular pressure is presently unknown but likely involves the circulation to the eye since administration of the calcium channel blocker nifedipine attenuates the increase [89]. Administration of succinylcholine to patients presenting with penetrating eye injuries has the potential to result in loss of global contents. In humans, controversy exists as to whether administration of a non-depolarizing NMBA prior to succinylcholine prevents the increase in intraocular pressure. However, since most domestic animals are easily intubated without the aid of a NMBA, it is probably prudent to avoid succinylcholine in veterinary patients presenting with penetrating eye injuries. It is important to realize that any induction technique which provokes gagging or forceful coughing will also raise intraocular and intracranial pressure and thus must be avoided in patients presenting with an open globe. Thus induction with a rapid and smooth-acting injectable anesthetic agent is crucial, making certain that adequate anesthetic depth has been achieved prior to attempting tracheal intubation.

Intragastric pressure

The administration of succinylcholine causes an initial depolarization of the motor endplate that is manifest clinically as fasciculations of the skeletal muscles. The muscle fasciculations cause abdominal compression and a resultant increase in intragastric pressure. The increase in intragastric pressure could theoretically increase the incidence of regurgitation and may worsen outcome in dogs presenting with gastric dilation volvulus.

Intracranial pressure

The transient muscle fasciculation induced by succinylcholine may be responsible for the increase in intracranial pressure seen following its administration. In humans the increase in intracranial pressure may be prevented by prior administration of the non-depolarizing NMBA d-tubocurarine. Again, since most domestic animals are usually readily intubated without use of a rapid-acting NMBA, it is recommended that succinylcholine be avoided in patients presenting with raised intracranial pressure. As with penetrating eye injuries, a rapid smooth induction of anesthesia free of coughing and struggling is desirable to prevent unnecessary increases in intracranial pressure.

Muscle responses

Administration of succinylcholine is often associated with postanesthetic muscle soreness. It has been suggested that this postanesthetic myalgia results from muscle fasciculation that occurs during the initial depolarization of the motor endplate [90]. Further, there appears to be good correlation between the intensity of the fasciculation and the intensity of the muscle pain [91]. Although skeletal muscle enzymes such as creatine kinase increase in both humans [92,93] and animals[94] following administration of succinylcholine, it is presently unknown if animals experience muscle pain similar to that of humans.

Muscle relaxants in anesthetized animals

Most animals can be intubated relatively easily without paralysis, and muscle relaxation caused by inhalant anesthetic agents is adequate for most procedures. While human patients are frequently given muscle relaxants to facilitate endotracheal intubation and surgical access, the use of muscle relaxants in veterinary practice is not as common. When considering use of NMBAs, veterinarians should first become familiar with their pharmacology and the clinical implementation of mechanical ventilation in

addition to developing skills at monitoring depth of anesthesia in paralyzed patients.

Indications

Muscle relaxants may be administered for numerous reasons. They are typically given with hypnotic drugs to eliminate laryngeal spasm and facilitate 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 non-paralyzed patient because some 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, the reason for paralysis, the duration, the health status of the patient, and concurrent drug administration. Relaxants will differ in the onset and duration of action, 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 [38,39].

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 [95]. 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 [96, 97]. 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 can be monitored during the anesthetic and recovery periods to minimize overdosing and residual paralysis.

Impaired metabolism and excretion

Hepatic insufficiency may alter the initial effect of non-depolarizing muscle relaxants because of an increase in the volume of distribution. However, their effect may be increased due to decreased elimination, especially when drugs dependent on hepatic biotransformation (e.g. vecuronium) are administered [98–100]. Impaired liver function may also prolong or cause residual neuromuscular blockade [101]. In general, muscle relaxants are not highly protein bound to albumin, typically less than 50% [102–105]. 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 [106]. 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 [107–110]. Recovery from mivacurium administration may also be prolonged, possibly because of decreased pseudocholinesterase activity [111]. Atracurium pharmacokinetics are generally unaffected, but if a constant-rate infusion is given to a patient with renal failure, laudanosine levels may be increased [112]. 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 [113]. 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 [114]. 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 [114]. 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 [114].

Acid–base disturbances

Generally, respiratory acidosis increases the intensity of muscle blockade, whereas respiratory alkalosis decreases the effect [115–118]. Both metabolic acidosis and alkalosis may potentiate the effects of muscle relaxants and make it more difficult to antagonize relaxant-induced muscle paralysis [115,116,118,119].

Electrolyte disturbances

Alterations in serum concentration of potassium, magnesium, and calcium influence neuromuscular blockade. Decreases in extracellular potassium result in hyperpolarization of the endplate and resistance to ACh-induced depolarization [120]. A relative increase in extracellular potassium lowers the resting membrane potential, opposing the effect of the muscle relaxant [120]. 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 [121]. Hypocalcemia decreases ACh release, muscle action potential, and muscle contraction strength, thus increasing the effect of the neuromuscular block [120,122]. Typically, hypercalcemia decreases the effect of d-tubocurarine, pancuronium, and possibly other NMBAs, resulting in a higher dose requirement to achieve paralysis [120].

Hypothermia

This generally slows drug elimination and decreases nerve conduction and muscle contraction. The overall clinical effect will vary with the degree of hypothermia and the NMBA administered.

Age

Youth is associated with altered dose requirements of muscle relaxants. Receptor immaturity and decreased clearance appear to increase the potency of muscle relaxants in the young [123–125]. 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, younger animals experience a faster onset of drug action while neuromuscular function recovers more quickly, so a lower dose of antagonist is usually required at the termination of the procedure [126].

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 [127,128].

Neuromuscular disorders

Animals with neuromuscular disorders may exhibit unpredictable responses to both depolarizing and non-depolarizing 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 non-depolarizing muscle relaxants because of neural damage and the possibility of denervation-induced upregulation [129]. These patients may also be predisposed to succinylcholine-induced hyperkalemia [130]. Diseases such as tick paralysis and botulism impair presynaptic release of ACh. Patients with presynaptic neuromuscular disorders show an increased sensitivity to non-depolarizing 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 endplate 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 non-depolarizing relaxants and have an increased sensitivity to succinylcholine-induced Phase II block [131,132]. These patients do not appear to be more sensitive to succinylcholine-induced hyperkalemia or malignant hyperthermia [133]. 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 [134,135].

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 [136,137]. Antagonism with either neostigmine or calcium may be difficult and unreliable [137]. Aminoglycosides, 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 [137]. Studies in anesthetized cats and horses given atracurium have shown a significant decrease in twitch tension after administration of gentamicin (2 mg/kg IV), but recovery times were not significantly changed [138,139]. Cats given gentamicin (10 mg/kg IV) during neuromuscular blockade have shown a significant decrease in tibialis cranialis twitch response [140]. 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 [141].

Tetracycline administration presumably depresses ACh release through calcium chelation. The enhanced blockade is usually reversible with calcium, but not neostigmine administration [137]. 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 [137]. 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 [137]. Penicillins and cephalosporins appear to have a negligible effect on overall neuromuscular function [137]. 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 β-blockers, doxapram, anticonvulsants, steroids, and H_2 receptor antagonists [114].

Monitoring neuromuscular blockade

Neuromuscular function may 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 important 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. 14.1).

Sites of stimulation

Sites for stimulation of peripheral motor nerves in dogs and cats include the peroneal and ulnar nerves (Figs 14.2, 14.3). In horses,

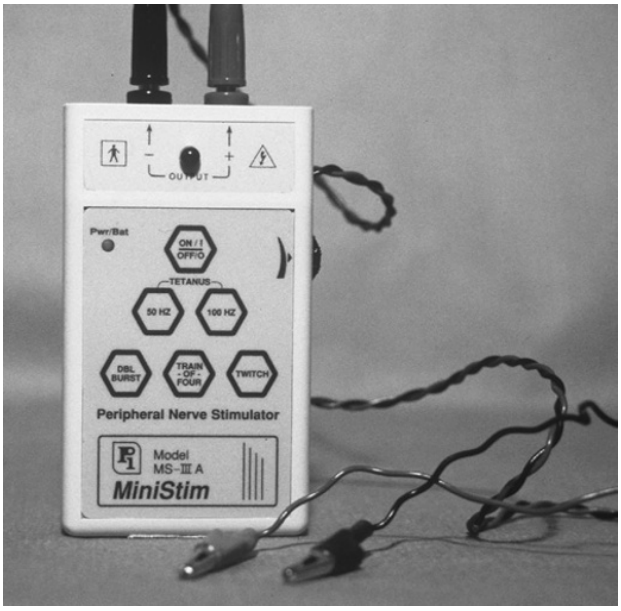

Figure 14.1 Peripheral nerve stimulator.

Figure 14.2 Superficial peroneal nerve stimulation in a dog.

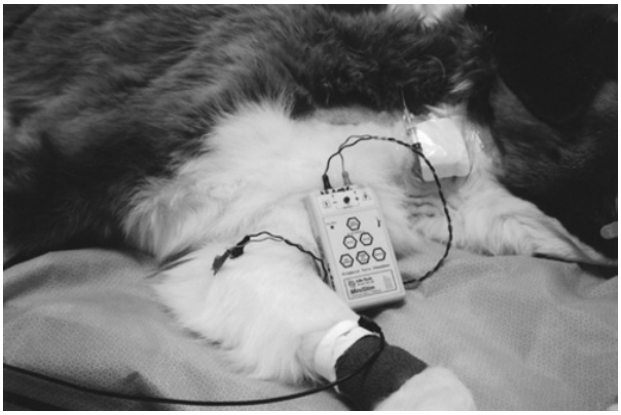

Figure 14.3 Ulnar nerve stimulation in a dog.

Figure 14.4 Facial nerve stimulation in a horse.

Figure 14.5 Peroneal nerve stimulation in a horse.

the facial nerve and superficial peroneal nerve are most commonly used (Figs 14.4, 14.5). Contact electrodes are placed over the nerve to be stimulated, and the resultant motor response is compared with the prerelaxant response.

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 0.2–0.3 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.

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

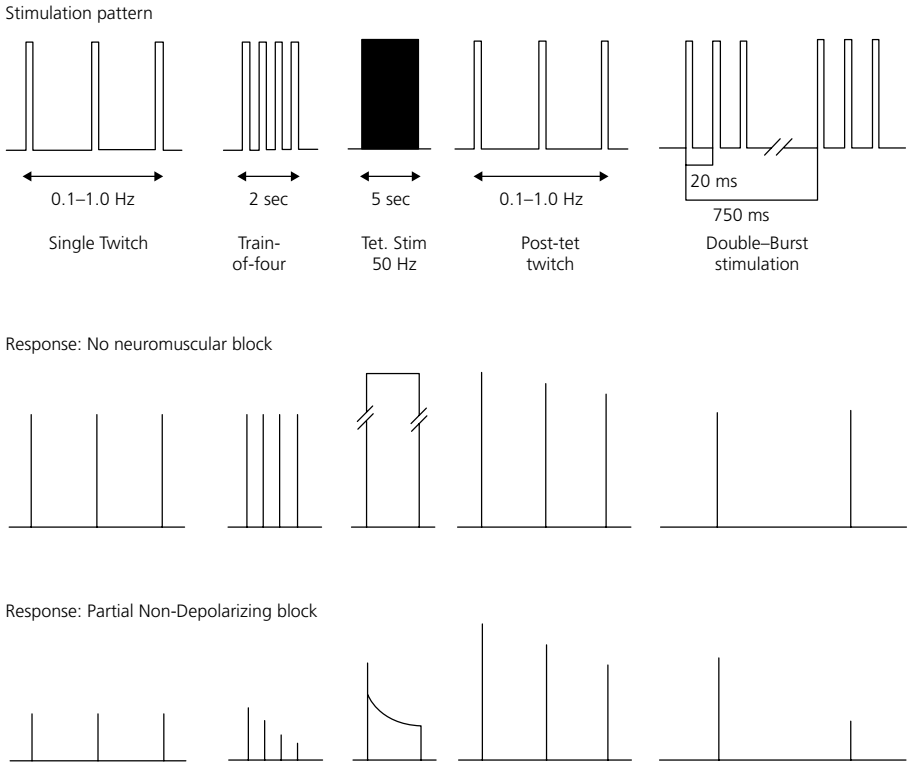

Figure 14.6 Different peripheral nerve stimulation patterns for monitoring neuromuscular function (*top panel*). Under each pattern is shown the characteristics of the evoked muscle responses measured mechanically before (*center panel*) and during (*bottom panel*) partial block.

administration of a muscle relaxant are presented in Fig. 14.6. Partial neuromuscular block with depolarizing and non-depolarizing relaxants modifies the recorded responses to these stimulation patterns. These modified responses are summarized in Table 14.3.

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 7–10 s [142]. 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 75–80% of receptors are blocked and will be abolished when approximately 90–95% of receptors are blocked [143].

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 10–20 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 [144]. 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 [145].

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 (see Table 14.3) [146].

Table 14.3 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.

Tetanic stimulation

Sustained muscle contraction is achieved by continuously delivering a high-frequency (50 Hz) supramaximal stimulus for 5 s [146]. Partial neuromuscular blockade from non-depolarizing relaxant administration will reduce tetanic height and cause fade [147]. 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 [148].

Post-tetanic facilitation

Post-tetanic 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 [143]. It is characterized by either an increase in twitch strength or a decrease in the degree of fade in response to a single-twitch, TOF, or double-burst pattern of stimulation. Post-tetanic facilitation is often the first clinical indicator of recovery from neuromuscular blockade [149,150].

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 [143]. An additional advantage of DBS is that D_1 is detectable at a deeper level of neuromuscular blockade than is T_1 [151].

Quantifying evoked responses

Whenever a muscle relaxant is administered, patients should 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 [49,138,139,152–154]. 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 100–300 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 [155].

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 [155]. 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 [156]. 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

Non-depolarizing 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 non-depolarizing muscle relaxants are antagonized by administering an anticholinesterase (also known as an acetylcholinesterase inhibitor). This class of drug inhibits the enzyme acetylcholinesterase, increasing the concentration of ACh molecules at the neuromuscular junction. Since non-depolarizing 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 non-depolarizing neuromuscular blockade [157]. The duration of action is similar for both neostigmine and edrophonium, whereas that of pyridostigmine is approximately 40% longer [157,158]. In cats, neostigmine is 12 times more potent than edrophonium [159].

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 reversal 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–placenta 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 activity. The administration of an anticholinesterase would actually prolong the depolarizing block [160]. On the other hand, a Phase II block from succinylcholine can be antagonized similarly to the non-depolarizing muscle relaxants, emphasizing the need for determining the type (Phase I or Phase II) of block present when using succinylcholine (see Table 14.3) [161,162].

Centrally acting muscle relaxants

Guaifenesin

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, brainstem, 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 [163]. Tissue can be damaged if guaifenesin is inadvertently administered perivascularly [163].

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 [164,165].

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 (2–3 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 [165]. Stallions may have up to 1.5 times longer action compared with mares. The longer recovery time in male horses is attributed to slower drug elimination from the plasma [166].

Guaifenesin has also been combined with thiobarbiturates or ketamine for use in cattle, small ruminants, and swine [167,168]. Although guaifenesin has been used in dogs, the large volume requirement makes it impractical for routine use in this species [169]. However, when combined with a thiobarbiturate or ketamine combined with xylazine, guaifenesin has proven an effective component when immobilizing dogs [170].

Dantrolene

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 [171]. Dantrolene is the drug of choice for the treatment of malignant hyperthermia. In swine, the recommended dose is 1–3 mg/kg IV when treating a malignant hyperthermia crisis and 5 mg/kg orally for prophylaxis [172]. 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 various sized 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 non-triggering 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 [173,174].

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 [175]. Severe myocardial depression has been reported when dantrolene is administered concurrently with verapamil or other calcium channel blockers [176,177]. Synergism, resulting in a delayed recovery of neuromuscular function, has been observed with dantrolene and vecuronium co-administration [178].

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