pneumoencephalogram); or both (as the distending limits of the compliant space are reached). Usually air is used to inflate the cuff of an endotracheal tube. This cuff is another relatively compliant, enclosed air space. Nitrous oxide will similarly expand this gas space and may increase the pressure exerted on the tracheal wall.

### *Occupational exposure: Trace concentrations of inhalation anesthetics*

Operating room personnel are often exposed to low concentrations of inhalation anesthetics. Ambient air is contaminated via vaporizer filling, known and unknown leaks in the patient breathing circuit, and careless spillage of liquid agent. Measurable amounts of anesthetic gases and vapors are present in operating-room air under a variety of conditions. Personnel inhale and, as shown by studies, retain these agents for some time. The slow rate of elimination of some vapors (especially the more blood-soluble agents like halothane) enables retained trace anesthetic quantities to accumulate from one day to the next.

Concern is raised because epidemiological studies of humans and laboratory studies of animals have suggested that chronic exposure to trace levels of anesthetics may constitute a health hazard. Of particular concern are reports that inhaled anesthetics possess mutagenic, carcinogenic, or teratogenic potential. Depending on the point in life at which exposure occurs, there is concern that these underlying mechanisms, in turn, may be responsible for an increased incidence of fetal death, spontaneous abortion, birth defects, or cancer in exposed workers. However, to date, no genotoxic effect of long-term or short-term exposure to inhaled anesthetics has been demonstrated in humans.

Although the data to date, especially regarding effects on human reproduction, remain equivocal, a firm cause-and-effect relationship between chronic exposure to trace levels of anesthetics and human health problems does not exist. Although the risk of long-term exposure to trace concentrations of anesthetics for those in operating room conditions appears minimal, current evidence is suggestive enough to cause concern and to encourage practices to reduce the contamination by anesthetics of operating room personnel. Indeed, exposure levels have been recommended by the government: 2.0 parts per million (ppm) for volatile agents and 25 ppm for $N_2O$. In this regard, inexpensive methods to reduce and control anesthetic exposure by operating room personnel are available and should be used.

## Muscle relaxants and neuromuscular blockade

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, $alpha_2$ adrenoceptor agonists, and guaifenesin. Although used frequently in human anesthesia and in some veterinary specialties such as ophthalmology, the use of NMBAs in general veterinary practice is limited.

### *Physiology of the neuromuscular junction*

All NMBAs 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 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. There appear to be two types of postjunctional receptors: junctional and extrajunctional. 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. 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. Extrajunctional receptors appear to be more responsive to depolarizing NMBAs such as succinylcholine and less responsive to nondepolarizing NMBAs such as atracurium. 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.

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. 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.

### *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. 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 repolarization 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, 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. 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. 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 2.3.

**Table 2.3.** Doses of commonly used NMBAs 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 | |

*Source*: Martinez E.A., Keegan R.D. 2007. Muscle relaxants and neuromuscular blockade. In: *Lumb and Jones' Veterinary Anesthesia and Analgesia*, 4th ed. W.J. Tranquilli, J.C. Thurmon, and K.A. Grimm, eds. Ames, IA: Blackwell Publishing, p. 423.

*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 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.

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. Additionally, species differences in pseudocholinesterase activity may exist. A reduction in plasma cholinesterase activity can be expected to prolong the action of succinylcholine.

*Pancuronium* Pancuronium was the first in a series of nondepolarizing NMBAs having a steroid nucleus. The drug has a dose-dependent onset of approximately 5 minutes and action ranging from 40 to 60 minutes in dogs. A large fraction of the drug is excreted by the kidney and the remainder is metabolized by the liver. 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 HR in some patients.

*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 minutes, and its action lasts approximately 30 minutes in dogs. Repeated doses do not tend to be cumulative, so neuromuscular blockade is sometimes maintained via continuous IV 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. 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 3.25–3.65. 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.

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. 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. Although signs of histamine release, such as hypotension and tachycardia, are not usually observed when atracurium is administered, slow IV administration is always preferred.

*Cisatracurium* Atracurium is a racemic mixture of 10 optical isomers. The 1R-cis, 1R9-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. 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.

*Vecuronium* Introduced in the 1980s, this was one of the first NMBAs free of cardiovascular effects. This drug has a dose-dependent onset of action of approximately 5 minutes and an intermediate duration of action similar to that of atracurium: 30 minutes. 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 hours. 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.

*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. Similar to vecuronium, rocuronium seems to be without cardiovascular effects and does not release histamine. The primary route of elimination is via the hepatic system while a small fraction is eliminated via the kidney.

*Doxacurium* This is a very potent benzylisoquinoline NMBA with a long duration of action. 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 minutes, 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. 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. Also, canine pseudocholinesterase enzyme might have differing affinity for the three primary isomers of mivacurium. Clinical observations indicate that mivacurium has a much briefer action in cats than in dogs.

### 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.

### Reversal of neuromuscular 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 carbamylester 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 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.

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. 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.

*Revised from "Cardiovascular System" by William W. Muir; "Respiratory System" by Wayne N. McDonell and Carolyn L. Kerr; "Nervous System" by Kurt A. Grimm and Anne E. Wagner; "Anticholinergics and Sedatives" by Kip A. Lemke; "Injectable and Alternative Anesthetic Techniques" by Keith R. Branson; "Dissociative Anesthetics" by Hui-Chu Lin; "Inhalation Anesthetics" by Eugene P. Steffey and Khursheed R. Mama; and "Muscle Relaxants and Neuromuscular Blockade" by Elizabeth A. Martinez and Robert D. Keegan in* Lumb & Jones' Veterinary Anesthesia and Analgesia, Fourth Edition.