Chapter 16

Neuromuscular blocking agents

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Many drugs used for induction or maintenance of anaesthesia provide a degree of skeletal muscle relaxation, but in general this is only mild to moderate at a surgical plane of anaesthesia. More profound muscle relaxation can be achieved in several ways:

- **Increasing the depth of anaesthesia.** Although muscle relaxation will improve with increasing depth of anaesthesia, this is not recommended because of the associated increase in cardiopulmonary depression
- **Local anaesthetic techniques.** By paralysing the motor fibres responsible for maintenance of muscle tone, the use of local anaesthetics can provide profound muscle relaxation (see Chapter 11). However, local anaesthesia may not be applicable or achievable in all cases, and considerable skill is required to perform some regional nerve blocks
- **Centrally acting muscle relaxants.** Benzodiazepines and alpha-2 adrenoceptor agonists both provide moderate to good muscle relaxation. However, because this effect is achieved via a centrally mediated action, they also have numerous other effects, many of which may be undesirable (see Chapter 13)
- **Peripherally acting muscle relaxants.** These are neuromuscular blocking agents (NMBAs) that act at the neuromuscular junction (NMJ) to provide profound skeletal muscle relaxation ('paralysis') throughout the body.

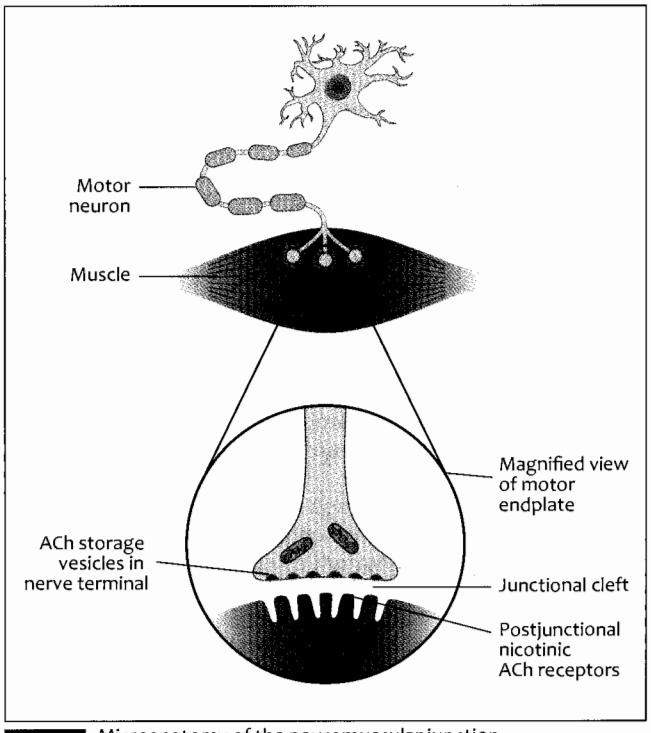
Although other drugs can be considered to be muscle relaxants due to their effects on the central nervous system (CNS) (see above), in general the term 'muscle relaxant' is most often used for NMBAs, and these form the focus of this chapter.

Microanatomy of the neuromuscular junction and physiology of neuromuscular transmission

An understanding of normal neuromuscular transmission is essential for the appropriate use of NMBAs.

Skeletal muscle cells are innervated by myelinated nerve fibres from motor neurons. As each nerve fibre approaches the muscle cell, it loses its myelin sheath. The region of contact between the nerve and the muscle is termed the *motor endplate* (Figure 16.1). Here, the muscle membrane becomes folded, and is separated from the nerve terminal by a distance of approximately 20 nm; this separation is known as the *junctional* (or *synaptic*) *cleft*. Within the nerve terminal there are abundant vesicles containing the neurotransmitter acetylcholine (ACh), and on the crests of the folded muscle membrane lie postjunctional nicotinic ACh receptors.

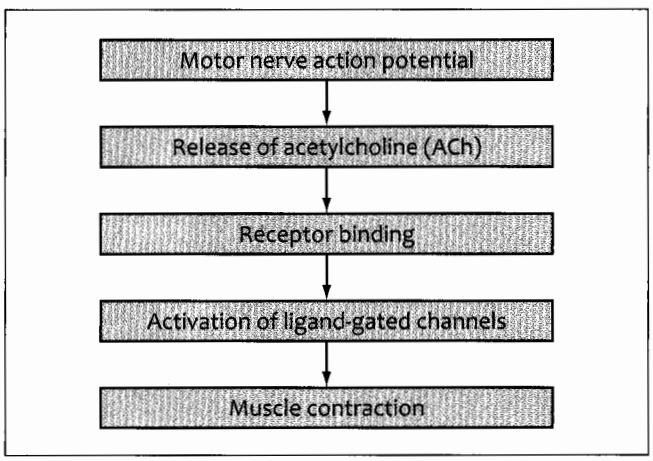
When an action potential reaches the nerve terminal, ACh storage vesicles in the terminal fuse to the prejunctional membrane and release ACh into the junctional cleft by exocytosis. ACh then diffuses across the cleft to bind to the postjunctional receptors. The receptors comprise a pentameric protein structure, which, when stimulated, undergoes a conformational change to open a transmembrane channel that allows movement of ions across the membrane. Two ACh molecules, binding to two distinct α-subunits of the pentameric structure, are required to open the ion channel. If one subunit is not bound, or is



16.1 Microanatomy of the neuromuscular junction. ACh = acetylcholine.

occupied by another molecule, the channel will not open. The movement of ions through the membrane channel generates an endplate potential, and if enough ion channels are opened, the adjacent muscle membrane depolarizes and an action potential is generated. Within the sarcolemma (muscle membrane), this action potential traverses the T-tubule system and causes release of calcium ions from the sarcoplasmic reticulum, initiating excitation–contraction coupling and subsequent muscle contraction (Figure 16.2).

Acetylcholine remains bound to its receptors for approximately 2 milliseconds, then detaches, and is rapidly hydrolysed into choline and acetate by the enzyme acetylcholinesterase, which is present in the junctional cleft. This terminates the action of ACh on the postjunctional receptors, the transmembrane channel closes and muscle contraction terminates.



16.2 Summary of events leading to normal muscle contraction.

There are also prejunctional nicotinic ACh receptors, which provide a positive feedback mechanism that augments ACh release during high-frequency nerve stimulation; that is, binding of ACh or an alternative agonist such as suxamethonium (succinylcholine) to these receptors stimulates further ACh release. However, the precise structure and function of the prejunctional receptors is less clearly defined than for those situated postjunctionally.

At physiological frequencies of nerve stimulation, neuromuscular transmission begins to fail only after a minimum of 75% of the postsynaptic ACh receptors have been blocked, and complete failure of transmission occurs with greater than 90% receptor blockade. This so-called neuromuscular 'margin of safety' implies that only 25% of ACh receptors need to be stimulated to induce normal neuromuscular transmission. The major implication of this is that during recovery from use of NMBAs, up to 75% of ACh receptors may still be blocked, with the patient exhibiting no detectable clinical signs, but with a reduced margin of safety.

Mechanism of action of neuromuscular blocking agents

Based on differences in their mechanisms of action, NMBAs can be classified as either *depolarizing (non-competitive)* or *non-depolarizing (competitive)*.

The only depolarizing relaxant used clinically is suxamethonium (succinylcholine), which consists of two molecules of ACh joined together. Because of its structure, administration of suxamethonium causes the generation of an action potential through binding to postsynaptic ACh receptors. However, since suxamethonium is not metabolized by acetylcholinesterase, the drug remains bound to the receptors for a longer period of time than ACh does, until suxamethonium blood concentration has declined sufficiently for the drug to diffuse down its concentration gradient from the NMJ into the plasma, allowing restoration of normal neuromuscular transmission. Plasma degradation of suxamethonium is mediated through the enzyme pseudocholinesterase (plasma cholinesterase; also known as butyrylcholinesterase), which is distinct from acetylcholinesterase. The prolonged binding of suxamethonium to the ACh receptor prevents normal neuromuscular transmission. As a result, the observed clinical effect is one of initial muscle stimulation as a result of the initial action potential, which manifests as widespread transient muscle fasciculations throughout the body, followed by a longer period of muscle flaccidity. This normal pattern of suxamethonium-induced blockade is known as *phase I block* (phase II block is described later).

Non-depolarizing NMBAs have a chemical structure different from that of suxamethonium. Although they also bind to the postsynaptic ACh receptors, they do not induce channel opening and the consequent generation of an action potential. By preventing ACh reaching the receptors, they induce a competitive blockade, resulting in muscle paralysis. Thus, unlike suxamethonium, non-depolarizing relaxants do not produce initial muscle fasciculations before the onset of muscle relaxation. It is not necessary for both α-subunit binding sites within the pentameric receptor structure to be occupied by a non-depolarizing NMBA to result in paralysis; only one site needs to be occupied by the drug and the ion channel will remain closed, even if the other site is occupied by an ACh molecule.

It is important to emphasize that NMBAs are neither anaesthetic nor analgesic. It is therefore possible that, if these agents are used inappropriately, a patient may be paralysed but fully conscious. This must be avoided at all costs by closely monitoring the adequacy of anaesthesia (see later).

Pattern of neuromuscular blockade

As NMBAs paralyse all skeletal muscles within the body, including those responsible for respiration, *it is essential that facilities for controlled ventilation are available whenever these drugs are used.* Not all muscles are equally sensitive to NMBAs. The diaphragm and intercostal musculature in particular are relatively resistant; these are usually the first muscles to recover following administration of an NMBA. However, the muscles around the pharyngeal area are much more sensitive to the effects of NMBAs and take longer to return to normal function. Clinically, patients may appear to be ventilating adequately during recovery from neuromuscular blockade, but may develop upper airway obstruction once the endotracheal tube is removed.

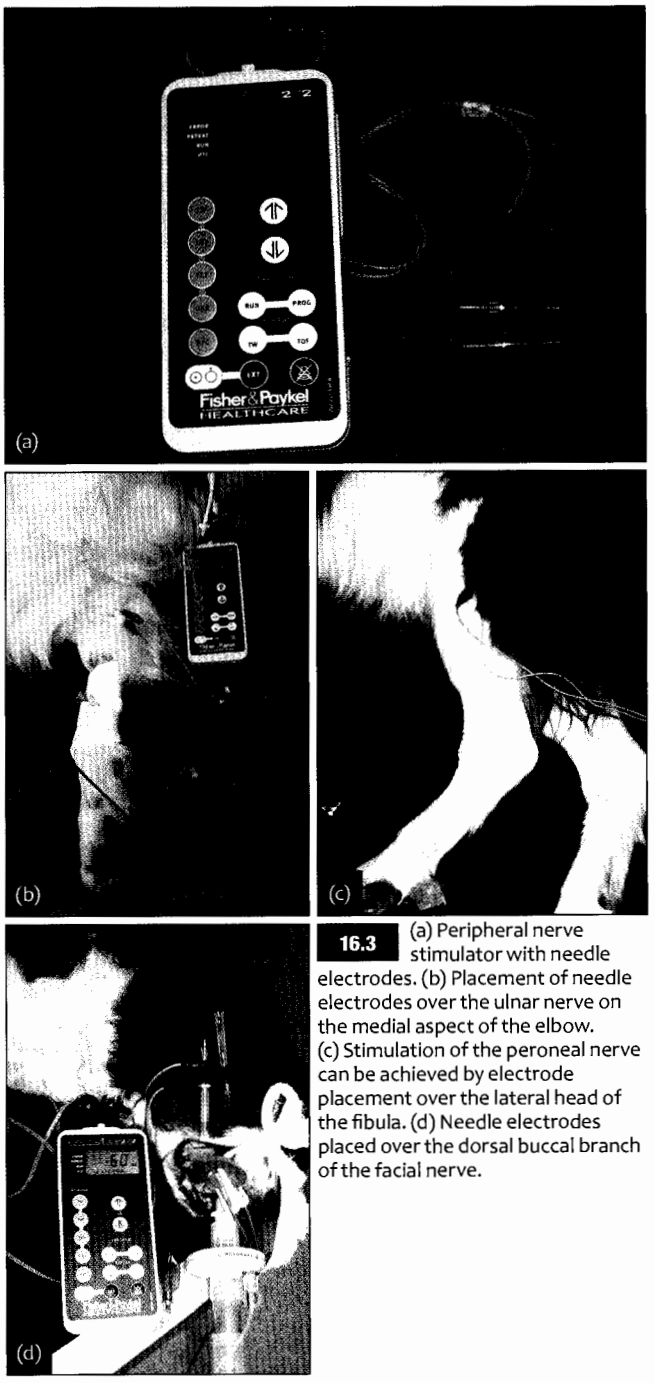
Because the diaphragm and intercostal muscles are less sensitive to NMBAs than other skeletal muscles in the body, attempts have been made to produce muscle relaxation without interference with respiratory function. An example is relaxation of the extraocular muscles to

produce a centrally positioned, immobile eye (for ocular surgery) by using low doses of NMBA, while maintaining spontaneous ventilation. This technique appears to avoid the need for either a staff member devoted to manual ventilation of the lungs, or an automatic ventilator (and associated expense). Although some authorities have claimed success with this practice, it involves considerable risk of hypoventilation of the patient, and, in the authors' opinion, should be avoided. As inspired oxygen concentration is often close to 100%, patients are usually able to maintain adequate oxygenation in these circumstances, but may become severely hypercapnic (Sullivan *et al.*, 1998).

Monitoring the neuromuscular junction

When using NMBAs, it is essential to assess the degree of neuromuscular blockade. This is most commonly performed by using a peripheral nerve stimulator (Figure 16.3a). This device delivers a small electrical current (up to 80 mA, depending on the model) through a pair of electrodes attached to the skin overlying a peripheral motor nerve. The ulnar nerve on the medial aspect of the elbow (Figure 16.3b), the peroneal nerve at the lateral head of the fibula (Figure 16.3c) or the dorsal buccal branch of the facial nerve caudoventral to the lateral aspect of the eye (Figure 16.3d) are most often used for stimulation. The response of the muscle groups innervated by these nerves is observed when the nerve stimulator is activated. The negative (black) electrode of the nerve stimulator should be positioned directly over the most superficial part of the nerve, while the positive (red) electrode is placed more proximally along the course of the nerve. The electrodes may be attached directly to the skin, or to subcutaneously placed needles. Although ECG electrode pads are normally used in humans as the interface for attachment of the nerve-stimulating electrodes, they seldom adhere sufficiently well to the skin of dogs and cats to prove reliable. It is important that the electrodes are attached over the nerve rather than the innervated muscle body, otherwise direct electrical stimulation of the muscle may occur, resulting in a muscle response even in the presence of complete neuromuscular blockade. Although techniques such as mechanomyography and electromyography are commonly used to assess the muscle response in research settings, they are too complex to be used clinically, and the veterinary surgeon (veterinarian) usually has to rely on visual and tactile assessment of the evoked muscle response (although clinically useful quantitative methods of assessment are becoming more widely available; see later).

The nerve stimulator should be capable of producing a square-wave pulse, with a constant current of at least 50–60 mA over a 1000 Ω load. The stimulus applied should be supramaximal to recruit all the nerve fibres: in the clinical setting, a supramaximal stimulus is usually achieved by increasing the nerve stimulator to the maximum current output, although lower outputs are probably still supramaximal if the current is being delivered via transcutaneous needles as opposed to ECG electrode pads. However, it is difficult to be sure that the stimulus is genuinely supramaximal merely by direct observation of the muscle response, so it remains customary to set the stimulator to its maximal output even when using needle



16.3 (a) Peripheral nerve stimulator with needle electrodes. (b) Placement of needle electrodes over the ulnar nerve on the medial aspect of the elbow. (c) Stimulation of the peroneal nerve can be achieved by electrode placement over the lateral head of the fibula. (d) Needle electrodes placed over the dorsal buccal branch of the facial nerve.

electrodes. The disadvantage of using excessive current as the stimulus is that it is proportionally more noxious in minimally anaesthetized animals.

Stimulation patterns

Several different stimulation patterns can be used to assess neuromuscular blockade.

Single twitch

The single twitch is a stimulation pattern that uses a single electrical pulse delivered at a rate between one per second (1 Hz) and one per 10 seconds (0.1 Hz). This pattern is principally used to assess onset of neuromuscular blockade, particularly when NMBAs are used to facilitate endotracheal intubation in humans, and has limited use in veterinary clinical anaesthesia.

Train-of-four

Train-of-four (TOF) is the most common pattern of nerve stimulation, and is used to assess both intraoperative neuromuscular blockade and recovery. Four electrical pulses are applied to the nerve over a 2-second period (i.e. 2 Hz). In the absence of neuromuscular blockade, four distinct muscle twitches will occur (T_1, T_2, T_3 and T_4), each of which is of identical strength (Figure 16.4a). If a non-depolarizing NMBA is then administered, the fourth twitch (T_4) in the TOF will become weaker and eventually disappear, followed by the third twitch (T_3), then the second (T_2) and eventually the first (T_1) if a sufficient dose is given (Figure 16.4bc). This phenomenon of a gradually decreasing muscle response to nerve stimulation during non-depolarizing NMBA-induced relaxation is known as fade (Figure 16.4b). The main cause proposed for the occurrence of fade with non-depolarizing NMBAs is that these drugs also block the prejunctional ACh receptors, thereby reducing the availability of ACh for release during high-frequency nerve stimulation.

Depolarizing NMBAs, in contrast, do not normally 'block' the prejunctional ACh receptors, but initially stimulate them in a similar way to the postjunctional receptors. The increased mobilization of ACh that results from prejunctional receptor stimulation may be partly responsible for the muscle fasciculations seen with depolarizing NMBAs before the onset of muscle relaxation. Given the absence of prejunctional ACh receptor blockade with depolarizing agents, fade is observed only with non-depolarizing agents, or in the presence of abnormal (phase II) suxamethonium blockade (see later). The TOF response to phase I suxamethonium blockade does not exhibit fade; instead, all four twitches are reduced to an equal extent.

With onset of non-depolarizing neuromuscular blockade, T_4 disappears when approximately 75% of ACh receptors are blocked; T_3 when approximately 80% are blocked; T_2 when around 90% are blocked; and loss of T_1 indicates essentially 100% blockade. During recovery, the twitches reappear in reverse order (i.e. T_1 first).

In addition to counting the number of muscle twitches in response to TOF (the 'TOF count') as a means of assessing the degree of neuromuscular blockade, attempts have been made (using mechanomyography in the research setting) to establish a TOF ratio (height of T_4:height of T_1) that indicates recovery of neuromuscular function to a degree that allows the patient adequate muscle strength for control of the airway. In humans, a TOF ratio of at least 0.9 is considered optimal before endotracheal extubation.

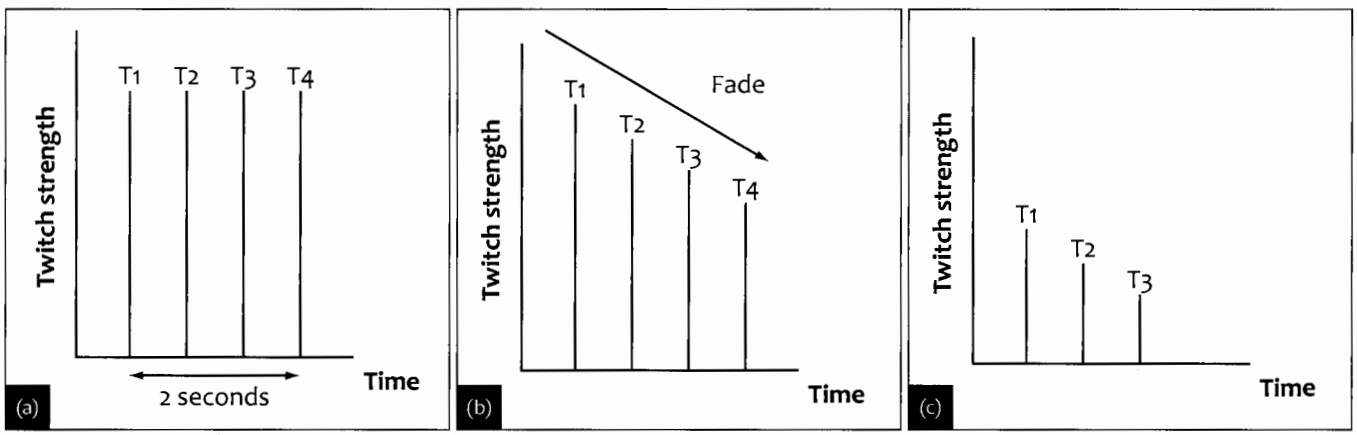
A number of studies have demonstrated that visual and tactile assessment of the TOF ratio is able to detect fade only when the TOF ratio is <0.4, implying that a significant degree of neuromuscular blockade may be missed by an observer in the clinical setting. This poor sensitivity of TOF in detecting residual neuromuscular blockade is probably related to the difficulty in comparing the strength of T_4 and T_1, while ignoring the two muscle twitches in between.

Tetanic stimulation

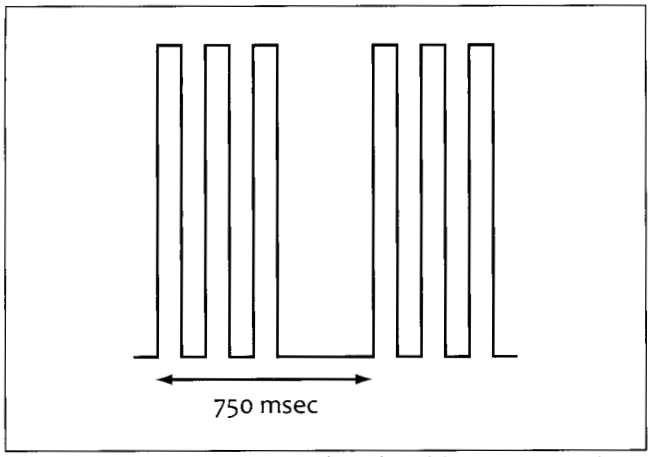
Tetanic stimulation ('tetanus') is defined as a sustained electrical stimulus of 50 Hz (occasionally 100 Hz) for a 5-second period. Because of the high frequency of stimulation, the muscle is unable to respond by producing 50 individual muscle contractions per second, but instead summates to produce one sustained muscle contraction. This pattern of stimulation is painful in the awake and minimally anaesthetized patient. Tetanic stimulation stresses the NMJ sufficiently that neuromuscular blockade can be detected by fade. As with TOF, tetanic fade can only be detected when significant degrees of neuromuscular blockade are present; the absence of obvious fade by visual and tactile assessment is not an indication of adequate neuromuscular transmission. Tetanic stimulation has principally been used to assess recovery from neuromuscular blockade, but due to the potential for severe pain, has largely been superseded by other stimulation patterns.

Double-burst stimulation

Double-burst stimulation (DBS) (Figure 16.5) comprises three short pulses at 50 Hz, followed by either three further 50 Hz pulses ($DBS_{3,3}$) or two 50 Hz pulses ($DBS_{3,2}$). The resultant muscle response is characterized by two individual muscle twitches (D_1 and D_2), which are stronger than those produced by TOF. The ratio of D_2:D_1 in DBS correlates closely with the TOF ratio T_4:T_1. However, it is easier to detect fade with DBS than TOF, because the observer is comparing the strength of two successive twitches, D_2 and D_1, in DBS, but is comparing T_4 with T_1 in TOF, while attempting to ignore T_2 and T_3. Visual and tactile assessment of DBS twitches can detect fade at equivalent TOF ratios <0.6. Thus, although DBS is superior to TOF for detection of residual neuromuscular blockade, it does not completely rule out the presence of residual blockade, since a TOF ratio ≥0.9 is required to ensure adequate neuromuscular recovery. DBS is used to assess recovery from neuromuscular blockade when there is no apparent fade to TOF (Figure 16.6).



16.4 Train-of-four (TOF) stimulation pattern. (a) Normal animal, no neuromuscular blockade. All four twitches in the TOF are present and of equal strength. (b) Onset of non-depolarizing blockade. Fade is present in the TOF but all twitches are still perceptible. (c) Neuromuscular blockade is now more profound: the fourth twitch in the TOF (T_4) has disappeared and the remaining three twitches are weaker.



16.5 Double-burst stimulation ($DBS_{3,3}$). Each burst comprises three stimuli at a frequency of 50 Hz with the second burst following 750 milliseconds after the first. In the absence of neuromuscular blockade, this produces two distinct muscle twitches.

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16.6 Main use of different peripheral nerve stimulation patterns. TOF is the most effective means of assessing depth of neuromuscular blockade. DBS is the most effective means of assessing recovery from neuromuscular blockade (i.e. the most reliable detector of fade).

Use of peripheral nerve stimulation

It is important to emphasize that peripheral nerve stimulation provides an indication *only* of the degree of neuromuscular blockade present – it gives no information on adequacy of anaesthesia. Therefore, a patient may have no response to nerve stimulation, but still be fully conscious.

The nerve stimulator should be placed over an appropriate peripheral nerve (see above), and correct function confirmed by observing muscle twitches during activation of the device, before administration of the NMBA.

Peripheral nerve stimulation serves two useful purposes. Firstly, it has been shown in humans that ideal muscle relaxation for abdominal surgery is achieved when only one or two twitches remain in the TOF (80–90% of receptors blocked). This allows the dose of NMBA to be titrated to achieve suitable surgical conditions. Secondly, at the end of surgery, it enables an assessment of residual neuromuscular blockade. In the absence of a *quantitative* technique of evaluation of blockade (see later), the TOF should have recovered to four equal-strength twitches, and no fade should be detectable on DBS, before the animal is allowed to recover from anaesthesia and the endotracheal tube removed. It is important to recognize that, because individual muscle groups have differing sensitivities to NMBAs (see above), monitoring the response to ulnar nerve stimulation, for instance, will give limited information on the muscles of respiratory function. Consequently, even with apparently adequate recovery of neuromuscular function on nerve stimulation, the patient must be closely observed in the immediate post-anaesthetic period to ensure adequate airway control and ventilation.

Quantitative monitoring of neuromuscular function

Visual and tactile assessment of the motor response to direct nerve stimulation, as described above, provides only a subjective measure of the degree of neuromuscular blockade; that is, it is non-quantifiable. More recently, however, techniques that allow more effective objective assessment of the degree of neuromuscular blockade have been developed. While some of these, such as mechanomyography and electromyography, are largely limited to laboratory-based situations, the technique of acceleromyography has achieved clinical utility.

Acceleromyography uses a small piezoelectric transducer, which is attached to a digit or distal limb of the patient. A current is then passed through the motor nerve supplying that site (in the same way as a 'traditional' peripheral nerve stimulator), producing a muscle response in the innervated area. This muscle movement generates a voltage change in the attached transducer that is proportional to the acceleration developed in the contracting muscle. The force generated by the contracting muscle is calculated automatically by the acceleromyograph on the basis of Newton's second law (force = mass x acceleration), given that the mass of the muscle is constant, and the acceleration has been measured by the machine. Devices based on this concept are now commercially available (e.g. TOF-Watch®) (Figure 16.7). These devices provide a quantitative measure of the TOF ratio and display a numerical value for the ratio, thereby eliminating reliance on visual and tactile assessment of the muscle response. Consequently, they dramatically reduce undiagnosed fade. This allows the clinician to ensure that the TOF ratio is at least 0.9 before the patient's trachea is extubated. In the coming years, it is likely that quantitative measures of neuromuscular blockade will become more common.

16.7 Acceleromyography using stimulation of the ulnar nerve, with the transducer attached to the palmar aspect of the metacarpus. Note that the leg is fixed in place using tape across the distal antebrachium: this is essential to ensure accuracy of the technique. In this case, the dog was recovering from rocuronium-induced neuromuscular blockade, and the acceleromyograph is displaying a TOF ratio of 90% (0.9), indicating that neuromuscular function has recovered sufficiently to allow endotracheal extubation.

Clinical assessment of recovery from neuromuscular blockade

Although the clinical monitors based on acceleromyography help to identify residual neuromuscular blockade ('curarization') at the end of anaesthesia, they cannot provide an absolute guarantee of adequate neuromuscular function. In addition, these devices are not universally available. Many veterinary anaesthetists still rely on the subjective peripheral nerve stimulation assessment methods described earlier, which at best can only detect TOF ratios <0.6; using such techniques, significant degrees of paralysis may still be present but undetectable.

Since the most serious consequences of residual neuromuscular blockade are hypoventilation and/or loss of airway control, many clinical tests of recovery have focused on assessing tidal volume or minute volume. However, diaphragmatic and intercostal muscle activity may have returned to normal even in the presence of significant degrees of weakness in other muscle groups, since the former are relatively resistant to the effects of NMBAs. As a result, patients may have a normal tidal volume but have limited control of the upper airway musculature, and may be unable to maintain airway patency after tracheal extubation. Thus, the presence of a normal tidal volume during recovery from neuromuscular blockade gives very little information about the degree of residual block in non-respiratory skeletal muscles. Similarly, a normal end-tidal carbon dioxide value on capnography gives no indication of the adequacy of upper airway muscle strength.

Other tests that are occasionally used in humans, such as assessment of vital capacity and maximum negative inspiratory pressure, are more difficult to utilize or interpret in conscious animals. Although maximum negative inspiratory pressure can be measured in anaesthetized animals by occluding the reservoir bag attachment to the breathing system and observing on a manometer the maximum negative pressure generated during inspiration, there is a potential risk of inducing negative-pressure pulmonary oedema with this technique and it is not recommended.

Monitoring adequacy of anaesthesia

Although some studies have suggested that the use of NMBAs may reduce anaesthetic requirements (presumably through reduction in afferent input to the CNS as a result of the loss of normal muscle tone), this is controversial. The animal must always be closely observed for signs of inadequate anaesthesia.

It is more difficult to assess the depth of anaesthesia in animals that have received NMBAs because many of the signs and responses normally monitored during anaesthesia (see Chapter 7) are absent or modified in these patients. For example, while the eye normally rotates ventromedially at surgical planes of anaesthesia in the cat and dog, neuromuscular blockade of the extraocular muscles causes the eye to remain centrally positioned. Similarly, although the presence or absence of the palpebral reflex is often used to quantify the depth of anaesthesia, paralysis of the periocular muscles obliterates this response, and no blinking occurs when the eyelids are stimulated. Paralysis of the respiratory musculature, which makes mechanical ventilation necessary, also abolishes any alterations in spontaneous ventilatory pattern that might otherwise be observed in response to nociceptive stimulation during a light plane of anaesthesia. Gross movement – the most classical sign of inadequate anaesthesia – is, of course, impossible when NMBAs have been administered.

Assessment of anaesthetic depth in patients that have received NMBAs therefore presents some challenges, but alterations in sympathetic nervous system activity will usually provide a useful guide to the adequacy of anaesthesia and/or analgesia. In general, patients that are too lightly anaesthetized or receiving inadequate analgesia, tend to be tachycardic and hypertensive, although a small number of cases may become bradycardic and hypotensive. In addition, patients may salivate excessively and demonstrate increased tear production and dilation of the pupils. End-tidal carbon dioxide values may also increase and isolated muscle twitching may occur, particularly on the extremities, tongue or oral commissures (Figure 16.8). This muscle twitching can occur even in patients in which there is no response to nerve stimulation. Although various theories have been proposed to explain this apparent anomaly, there is currently no universally accepted explanation. Many modern anaesthetic monitors display information on the end-tidal anaesthetic agent concentration, which provides useful information on approximate anaesthetic depth, and should help to minimize the incidence of inadequate anaesthesia and patient awareness during NMBA use.

Patients that are excessively anaesthetized and have received NMBAs are likely to be hypotensive, and possibly bradycardic. However, too light a plane of anaesthesia must *also* be avoided, and every effort should be made to ensure the adequacy of anaesthesia in patients receiving NMBAs, since it is clearly unacceptable to have a patient aware but immobile.

It is important to reiterate that monitoring of neuromuscular transmission with a peripheral nerve stimulator gives *no* information whatsoever on anaesthetic depth.

- Increase in pulse rate
- Increase in arterial blood pressure
- Salivation
- Lacrimation
- Increase in end-tidal carbon dioxide partial pressure/concentration
- Muscle twitching, especially around the head

16.8 Signs of inadequate anaesthesia during neuromuscular blocking agent (NMBA) use.

Indications for the use of neuromuscular blocking agents

Deep surgical dissection

Neuromuscular blocking agents are extremely useful to relax the abdominal musculature, particularly for dissection deep within the abdomen, for example, nephrectomy and adrenalectomy. However, they will improve surgical conditions even for routine procedures, such as ovariohysterectomy. In addition, NMBAs may reduce the degree of postoperative discomfort by minimizing muscle resistance to abdominal stretching (e.g. by the use of surgical retractors), even though they themselves have no analgesic effects. They are also of value during spinal surgery (e.g. hemilaminectomy) in heavily muscled animals.

Thoracic surgery

Intermittent positive pressure ventilation (IPPV) is mandatory during intrathoracic surgery (see Chapters 6 and 23). Although not required in every case, the use of NMBAs allows a smooth transition from spontaneous to mechanical ventilation.

Dislocations and fractures

Neuromuscular blocking agents facilitate the reduction of dislocated joints. Although controversial, they may also improve surgical conditions during fracture reduction, especially in larger patients; this depends on the degree of muscle fibrosis resulting from the initial trauma.

Ophthalmic surgery

By relaxing the extraocular muscles, NMBAs produce a centrally positioned eye that protrudes slightly. This facilitates delicate ocular surgery. In addition, paralysis of the respiratory musculature means that the patient cannot resist IPPV; 'fighting' or 'bucking' the ventilator would be detrimental because the associated increase in intrathoracic pressure would significantly increase intraocular pressure. Neuromuscular blocking agents have no direct effect on pupillary size in cats or dogs because the iris is composed of smooth muscle, but they cause pupillary dilation in birds, where the ciliary muscle is striated. Further details on anaesthesia for ophthalmic procedures may be found in Chapter 19.

Endotracheal intubation

It is routine practice in cats to apply lidocaine to the larynx before attempting endotracheal intubation: this helps to avoid the development of laryngospasm. However, this technique imposes a time delay between induction of anaesthesia and establishment of a secure airway, because the local anaesthetic requires at least 60 seconds to achieve its peak effect. While this delay is usually well tolerated in healthy cats, those with respiratory impairment (e.g. diaphragmatic rupture) may become severely hypoxaemic during this period.

Relaxation of the larynx may also be achieved by using NMBAs. It is important that an adequate period of preoxygenation (100% oxygen by facemask for 3–5 minutes) is provided before administration of these drugs for the purpose of endotracheal intubation.

Although any NMBA may be used for this purpose, suxamethonium has traditionally been the most common choice because it has the fastest onset time (30–60 seconds). However, given the common side effects of suxamethonium (e.g. painful muscle fasciculations, cardiac arrhythmias), the non-depolarizing relaxant rocuronium may be preferred despite its slightly slower onset time. A number of studies in humans have suggested that when using rocuronium, rapid endotracheal intubation is best accomplished by using higher doses of the drug than those traditionally used for neuromuscular blockade; higher doses shorten the onset time by producing a higher concentration gradient for the drug to diffuse from the blood to the NMJ. In the authors' experience, administration of either suxamethonium or rocuronium to cats, immediately following the anaesthetic induction agent, allows endotracheal intubation in a significantly shorter time than when local anaesthesia is used to desensitize the larynx. In addition, use of an NMBA allows passage of a larger diameter endotracheal tube, since the rima glottidis will open more widely. *This is the only situation where muscle relaxants are administered before securing an airway by endotracheal intubation.*

Individual agents

Neuromuscular blocking agents should only be administered when:

- A patent airway has been established by endotracheal intubation (with the exception of suxamethonium/rocuronium for rapid intubation in cats, as described above)
- A stable plane of anaesthesia has been achieved
- Facilities for IPPV are immediately available
- Facilities for monitoring the degree of neuromuscular blockade are available.

In addition, secure intravenous access should be available throughout the procedure because all NMBAs and associated reversal drugs are administered by this route.

The onset time of NMBAs is inversely proportional to their potency, that is, those that require higher doses (lower potency) have faster onset times. However, this is of minimal clinical significance, as all NMBAs achieve their peak effect over the course of a few (approximately 1–3) minutes.

Many agents have been used to produce neuromuscular blockade over the years, but only those in current clinical use will be considered here.

Depolarizing relaxants

Suxamethonium

Suxamethonium is the only depolarizing agent currently in use. It has the fastest onset time of any muscle relaxant, and is generally relatively short-acting. However, repeated or high doses can lead to a *phase II block* (as opposed to the phase I block usually produced), where the neuromuscular blockade assumes some characteristics of a non-depolarizing block and becomes relatively long-acting. Phase II block can be detected by TOF monitoring because 'fade' develops, a characteristic not normally associated with suxamethonium-induced (phase I) blockade. Phase II block can develop in dogs following even a single dose of the drug, so it is seldom used in this species. The mechanism by which fade occurs during phase II suxamethonium block is not entirely clear, but it may be related to blockade of the prejunctional ACh receptors by the drug, thereby limiting mobilization of ACh to its release sites on the nerve terminal.

Suxamethonium has a number of other side effects that limit its usefulness. In particular, cardiovascular effects can be marked, with either bradycardia or tachycardia arising, as well as arterial hypertension. Cardiac arrhythmias may also occur. Because of the initial muscle fasciculations produced before onset of blockade, suxamethonium is thought to cause muscle damage, and an increase in plasma potassium concentration (by up to 0.5 mmol/l usually) may be observed. This increase may be clinically significant in patients with pre-existing hyperkalaemia, such as cats with urinary obstruction. The muscle fasciculations are associated with significant post-anaesthetic pain in humans, and it is reasonable to presume that this also occurs in animals. Suxamethonium can also increase

intraocular pressure through sustained contraction of extraocular muscles, and can trigger malignant hyperthermia in susceptible patients, although this is rare.

Since incremental doses of suxamethonium may induce a phase II block, the drug should only be administered as a single dose. No antagonist agent for suxamethonium is available, and the duration of action is principally dictated by plasma cholinesterase levels, which vary widely between patients. As a result of these two factors, suxamethonium has limited use in veterinary anaesthesia, with the main (rare) indication being facilitation of endotracheal intubation in cats.

Dose:

- Dogs: 0.3 mg/kg i.v. provides approximately 25 minutes of relaxation. Not recommended (see above).
- Cats: 3–5 mg i.v. total dose for an adult cat provides approximately 5 minutes of relaxation.

Non-depolarizing relaxants

Non-depolarizing relaxants can be classified on the basis of their chemical structure as either benzylisoquinoline (curariform) derivatives or aminosteroids. The potency of all these agents is inversely related to their onset time; that is, the more potent the agent, the slower its onset. Incremental doses may be given as required, using approximately one-quarter to one-third of the initial dose. Their effects can be reversed with anticholinesterases (see below). Therefore, they offer much greater flexibility in use than suxamethonium. It is important to emphasize that the doses provided below for each drug are guides only, since patients vary widely in their requirements. Use of a peripheral nerve stimulator is the only accurate method of determining the necessary dose and the need for additional increments.

Benzylisoquinolines

Atracurium: Atracurium is degraded in the body both by non-specific esterases and by Hofmann elimination (a spontaneous breakdown process, which is both pH and temperature dependent), and <10% of the drug is excreted unchanged by the liver and kidneys. Consequently, the action of atracurium is independent of renal and hepatic function, and it is generally the NMBA of choice for patients with hepatopathy or nephropathy. Laudanosine, one of the products of Hofmann elimination of atracurium, has been associated with CNS stimulation and precipitation of seizures in the experimental setting. This is unlikely to be relevant clinically unless massive doses of atracurium were to be administered to a patient with concomitant renal and/or hepatic failure, since the plasma concentration of laudanosine observed after clinical doses of atracurium are significantly lower than those which produce these CNS effects. Although atracurium has the potential to release histamine (particularly with high doses given rapidly), this appears to be uncommon in animals. However, the drug is probably best avoided in patients where histamine release may be particularly detrimental, e.g. those with asthma. Due to its temperature dependent spontaneous degradation, atracurium should be stored in a refrigerator.

Dose:

- In cats and dogs, 0.25–0.5 mg/kg i.v. provides approximately 20–40 minutes of relaxation (although it is probably preferable to use doses at the lower end of the range, with increments as necessary). The drug is also suitable for infusion: an initial bolus of 0.25 mg/kg followed by an infusion of 0.4–0.5 mg/kg/h, started immediately after the bolus dose. The infusion should be prepared in 0.9% sodium chloride or 5% dextrose to minimize Hofmann degradation.

Cisatracurium: Cisatracurium is one of 10 stereoisomers of atracurium. It is eliminated in a similar way by Hofmann degradation, but not by non-specific esterases. Cisatracurium is more potent than atracurium, and has a lower propensity to release histamine. Because of its greater potency, less cisatracurium is required to produce an equivalent degree of neuromuscular blockade, and consequently less laudanosine is produced in comparison with atracurium.

Since histamine release is uncommon in animals following atracurium administration, and since the clinical significance of laudanosine production is probably minimal (see above), the precise advantages of cisatracurium in veterinary anaesthesia are unclear. It may be the relaxant of choice in patients that are at risk from histamine release and additionally have concurrent hepatic disease. The effects of cisatracurium appear to be fairly unpredictable in animals.

Dose:

- Dogs: 0.15 mg/kg i.v. provides approximately 30 minutes of relaxation. Infusion rates of approximately 0.2–0.45 mg/kg/h following the initial bolus dose have also been used successfully.
- Cats: to the authors' knowledge, there are no published reports of the clinical use of cisatracurium in cats.

Mivacurium: Mivacurium is unique among non-depolarizing NMBAs in that it is metabolized by plasma cholinesterase, at a rate of approximately 70–88% that of suxamethonium (in humans). This produces a short duration of neuromuscular blockade. In addition (and unlike suxamethonium), mivacurium can be antagonized readily with anticholinesterases (see below). Although there is very limited information on its clinical use in animals, this agent has provided rapid-onset, medium-duration relaxation in cats. In dogs, however, mivacurium has a long duration of action unless administered at very low doses, although it does appear to be free of significant haemodynamic effects. It would seem, therefore, that mivacurium offers little benefit in animals over the more commonly used NMBAs such as atracurium and vecuronium.

Dose:

- Dogs: 0.01 mg/kg, 0.02 mg/kg and 0.05 mg/kg i.v. provide relaxation for approximately 34, 65 and 151 minutes, respectively.
- Cats: 0.1 mg/kg i.v. provides approximately 25 minutes of relaxation.

Aminosteroids

Vecuronium: Vecuronium has negligible effects on the cardiovascular system, even at high doses. It undergoes hepatic metabolism, with biliary and urinary excretion of both the parent compound and metabolites; the principal metabolite, 3-desacetylvecuronium, has approximately 80% of the potency of vecuronium, and is of longer duration. Prolonged effects of vecuronium may be observed with either hepatic or renal disease. Vecuronium is supplied in a lyophilized form, which is dissolved in sterile water for injection; the resultant solution is stable at room temperature for approximately 24 hours.

Dose:

- In cats and dogs, 0.1 mg/kg i.v. provides approximately 20 minutes of relaxation. Vecuronium can also be administered by intravenous infusion, with an initial bolus dose of 0.1 mg/kg followed immediately by infusion at a rate of 0.1 mg/kg/h.

Pancuronium: Pancuronium is a relatively long-acting NMBA. It can induce tachycardia and hypertension through a vagolytic and mild indirect sympathomimetic action. It is seldom used in current veterinary practice as the preference is now to use shorter-acting NMBAs with fewer cardiovascular side effects which are administered in increments as required.

Dose:

- In cats and dogs, 0.06 mg/kg i.v. provides approximately 45–60 minutes of relaxation.

Rocuronium: Rocuronium is a short- to intermediate-acting NMBA. It produces minimal cardiovascular side effects, although it occasionally causes mild increases in heart rate and blood pressure. It has the fastest onset among the non-depolarizing agents when used at the higher range of reported doses, being only slightly slower than suxamethonium, but this appears to be its only real advantage over other agents.

Dose:

- Dogs: 0.5–0.6 mg/kg i.v. provides approximately 15–30 minutes of relaxation. An infusion of 0.2 mg/kg/h started immediately after the initial bolus may be used to maintain relaxation.
- Cats: 0.6 mg/kg i.v. provides approximately 15 minutes of relaxation. A higher dose is required if rocuronium is used to achieve endotracheal intubation, and the authors usually use 1.2–1.5 mg/kg i.v. for this purpose.
- There are no reports of the use of this drug by infusion in cats.

Short-acting and long-acting NMBAs

It has been demonstrated in humans that shorter-acting NMBAs are more easily antagonized than longer-acting agents. Therefore, for procedures where relaxation may be required for a relatively long period of time, it is now more common to administer short- or intermediate-duration agents, such as atracurium, rocuronium or vecuronium, and to provide incremental doses as required, rather than to use longer-acting agents such as pancuronium.

Interactions between neuromuscular blocking agents and other drugs

A number of drugs may interact with NMBAs when administered concurrently:

- **Volatile anaesthetic agents.** These potentiate the effects of NMBAs both in terms of dose requirements and duration of action. Although the results of studies vary to some extent, depending on both the species and patient's age, sevoflurane appears more potent or equipotent to isoflurane in this regard, while isoflurane exhibits greater potentiation than halothane. With all the volatile agents, atracurium and vecuronium appear to be potentiated less than pancuronium
- **Injectable anaesthetic agents.** At clinical doses, propofol appears to have minimal effect on the action of NMBAs. Ketamine potentiates all non-depolarizing NMBAs in a dose-dependent manner in a primate model
- **Antibiotics.** Some antibiotics may prolong neuromuscular blockade by mechanisms that vary from agent to agent. Several sites at the NMJ may be affected. The most important antibiotics in this regard are the aminoglycosides, although the effect produced varies depending on the NMBA used, the concentration of the antibiotic achieved *in vivo*, and variability between patients. Close monitoring of the NMJ is certainly recommended if aminoglycosides and NMBAs are used concurrently during anaesthesia. Some studies have shown that administration of calcium salts may be useful to reverse any prolonged blockade that occurs when these agents are used together; however, others have suggested that the use of calcium is inappropriate as its effect will not be sustained (and the patient may therefore redevelop neuromuscular blockade), and also because calcium can antagonize the antibacterial effects of aminoglycosides
- **Anticonvulsants.** The interaction between anticonvulsants and NMBAs is complex and the mechanism by which it occurs is poorly understood. For example, acute administration of phenytoin (in humans) has been shown to augment neuromuscular blockade with rocuronium. Conversely, chronic administration of either phenytoin or carbamazepine appears to produce resistance to all of the aminosteroid NMBAs. Anticonvulsants appear to have minimal effects on the dose requirements and duration of the benzylisoquinolines
- **Histamine (H_2) receptor antagonists.** High-dose oral cimetidine prolongs vecuronium-induced blockade, while intravenous ranitidine has been shown to antagonize atracurium relaxation in rats, but not in humans. The clinical significance of the interaction between muscle relaxants and H_2 antagonists is unclear.

Use of neuromuscular blocking agents in the presence of concurrent disease

The presence of concurrent disease may influence the NMBA chosen, and may also require modification of the dose administered:

- **Renal and hepatic disease.** Atracurium (or cisatracurium) is generally the NMBA of choice for patients with renal or hepatic disease because of its unique method of degradation. Although renal elimination plays only a minor role in terminating the effects of vecuronium, studies in humans have demonstrated an increased duration of action in patients with renal failure
- **Acid–base and electrolyte disturbances.** The effects of acid–base disturbances on NMBAs are extremely

complex and vary between agents, but either potentiation or antagonism of NMBAs may occur. Electrolyte disorders have similarly complex effects, but, generally, hypernatraemia and hypokalaemia will potentiate non-depolarizing agents, while hyponatraemia and hyperkalaemia will antagonize them

- **Burn injuries.** Patients with extensive burns may develop resistance to non-depolarizing NMBAs, while administration of suxamethonium can produce severe hyperkalaemia and ventricular fibrillation. These effects generally occur within approximately 24 hours of the initial injury, and persist until complete healing of the wounds. The mechanism responsible is thought to be proliferation of extrajunctional ACh receptors in association with the burn injury
- **Spinal cord injury.** This may increase sensitivity to non-depolarizing agents, while administration of suxamethonium to these patients can induce hyperkalaemia
- **Myasthenia gravis.** Patients with myasthenia gravis are extremely sensitive to the effects of non-depolarizing NMBAs, and use of a nerve stimulator is mandatory if these agents are used in animals with this condition. An initial dose of approximately one-tenth of the normal dose should be used, and small incremental doses administered as dictated by TOF monitoring
- **Diabetes mellitus.** The duration of action of vecuronium is shorter in dogs with diabetes, as indicated by both tactile and electromyographic monitoring (Clark *et al.*, 2012).

Antagonism of neuromuscular blockade

Recovery from neuromuscular blockade may occur spontaneously, as the plasma concentration of relaxant diminishes (due to metabolism and elimination). This allows the drug to diffuse away from the NMJ, moving down its concentration gradient into the plasma. Alternatively, in the case of non-depolarizing NMBAs, recovery may be hastened by administration of an anticholinesterase. These agents inhibit the effects of the enzyme acetylcholinesterase, which is responsible for the rapid metabolism of ACh following its release. Consequently, anticholinesterases allow accumulation of ACh, which is then able to competitively displace the non-depolarizing NMBA from the postsynaptic ACh receptor, restoring neuromuscular transmission. Anticholinesterases will not reverse classic phase I suxamethonium blockade because the block induced is non-competitive (see earlier); there is some evidence, however, that they may facilitate reversal of a fully-developed phase II suxamethonium block.

Anticholinesterases not only allow ACh to build up at the nicotinic receptors of the NMJ but, in addition, ACh accumulates at postganglionic parasympathetic muscarinic receptors throughout the body. This may produce a number of unwanted side effects, such as bradycardia and cardiac arrhythmias, bronchoconstriction, salivation, defecation and diarrhoea. To prevent these muscarinic effects, anticholinesterases are usually administered in conjunction with antimuscarinic agents, such as atropine or glycopyrronium.

Two anticholinesterases are used clinically for reversal of non-depolarizing NMBA-induced relaxation: neostigmine and edrophonium. Neostigmine has a slow onset but long duration, whereas edrophonium has a more rapid onset but somewhat shorter duration of action. Of the antimuscarinic agents, atropine has a rapid onset and short duration of action, and glycopyrronium has a slow onset and long duration. Therefore, the pharmacokinetic profile of atropine fits more closely with that of edrophonium, while the profile of glycopyrronium fits more closely with that of neostigmine. It is therefore most logical to use either an edrophonium–atropine or neostigmine–glycopyrronium combination for reversal of neuromuscular blockade. A neostigmine–glycopyrronium combination is commercially available (Robinul-Neostigmine). However, even though the pharmacokinetics of neostigmine–glycopyrronium and edrophonium–atropine combinations are the most compatible, it is still not uncommon to see minor muscarinic effects when these combinations are used, particularly mild bradycardia or second-degree atrioventricular block. These effects are, however, usually transient. An edrophonium–atropine combination produces the fewest muscarinic side effects and is the combination of choice in patients where these effects may be detrimental, such as those with significant cardiac disease. Edrophonium is significantly more expensive than neostigmine, so the latter is more commonly used for antagonism of neuromuscular blockade, with edrophonium generally being reserved for specific situations where the more profound muscarinic effects of neostigmine might be problematic.

If a short-acting anticholinesterase (edrophonium) is used with a long-acting NMBA (e.g. pancuronium), there is an increased risk of recurarization in the recovery period; that is, the edrophonium may initially reverse the blockade and restore normal neuromuscular transmission, but because edrophonium is shorter acting than the relaxant, neuromuscular blockade may recur as the edrophonium concentration at the NMJ declines. Thus, if longer-acting NMBAs have been used, neostigmine is the anticholinesterase of choice because of its long duration of action. In addition, neostigmine more reliably antagonizes a more intense blockade than edrophonium. Neostigmine has, however, also been shown to possess neuromuscular-blocking capabilities, particularly if administered in high doses; consequently, the doses described below should not be exceeded.

The greater the TOF count (or TOF ratio if using objective monitoring techniques such as acceleromyography) before reversal, the more likely the success in restoring neuromuscular transmission, and the less likely the occurrence of residual neuromuscular blockade or recurarization during recovery. Consequently, where time allows, it is preferable to wait for restoration of all four twitches in the TOF before administering the antagonist agent. Although it is possible to achieve reversal when only one twitch has reappeared, it is less predictable, requiring higher doses of anticholinesterase, and with a greater potential for residual/re-curarization occurring later.

Inadequate reversal of neuromuscular blockade at the end of anaesthesia risks residual blockade in the recovery period, which may lead to serious consequences for the animal. Numerous studies in humans have demonstrated that patients commonly arrive at the recovery room with significant residual blockade still present, which is responsible for a higher incidence of complications, particularly those involving the respiratory system. The advent of more objective clinical methods for assessment of neuromuscular transmission, such as acceleromyography, may reduce the incidence of residual neuromuscular blockade during the recovery period.

Although reversal is not always required following the use of muscle relaxants, it should certainly be considered when longer-acting NMBAs have been used, or when multiple boluses or infusions of these agents have been delivered. If in doubt as to the patient's state of neuromuscular recovery, it is wise to err on the side of caution and administer an anticholinesterase.

Administration of anticholinesterases

Neostigmine and glycopyrronium are usually mixed in a ratio of 5:1 (2.5 mg neostigmine + 500 μg glycopyrronium/ml in the commercial preparation), with a total dose requirement of 0.01–0.05 mg/kg i.v. neostigmine, depending on the degree of neuromuscular blockade at the time of reversal.

Edrophonium and atropine are usually mixed in a 25:1 ratio (1 mg/kg edrophonium + 40 μg/kg atropine) and given by slow intravenous injection to effect over several minutes.

In preference to mixing the antimuscarinic agent and anticholinesterase in the same syringe, some veterinary surgeons instead administer the antimuscarinic 1–2 minutes before the anticholinesterase to lessen the risk of muscarinic side effects. However, cardiac instability may occur with this approach because the antimuscarinic agent generally induces a transient tachycardia before the heart rate reduces once the anticholinesterase is administered.

It is vital that both ventilatory support and a depth of anaesthesia adequate to prevent awareness are maintained until full reversal of neuromuscular blockade has been achieved. Failure to restore spontaneous ventilation may occur for several reasons (Figure 16.9).

- Ongoing neuromuscular blockade (in absence of a peripheral nerve stimulator):
  - Inadequate antagonism
  - Hepatic/renal disease
  - Acid–base/electrolyte disturbance
- Excessive anaesthetic depth
- Hypocapnia (over-ventilation)
- Hypothermia

16.9 Common causes of failure to restore spontaneous ventilation following the use of neuromuscular blocking agents (NMBAs).

Sugammadex

A specific non-depolarizing NMBA reversal agent, sugammadex, has relatively recently been licensed for use in humans in some countries. This agent is a modified cyclodextrin compound that works in a completely different way to the anticholinesterases. Cyclodextrins have a ring structure with a hydrophilic surface, which makes them water soluble, but with the capability to encapsulate hydrophobic molecules within their central core. Sugammadex was primarily developed as a reversal agent for rocuronium, although it also reverses (slightly less effectively) vecuronium-induced neuromuscular blockade (and, to a much lesser extent, also pancuronium). It is ineffective against benzylisoquinoline NMBAs. Sugammadex is highly efficient at rapidly 'mopping up' aminosteroid NMBA molecules, even during profound (or following prolonged) neuromuscular blockade. Once the rocuronium or vecuronium becomes encapsulated in the central core of the cyclodextrin molecule, it is no longer able to act at the NMJ. Since sugammadex antagonizes NMBAs without inhibition of acetylcholinesterase, muscarinic effects do not occur, and therefore the concurrent administration of antimuscarinic drugs is unnecessary. Sugammadex is also largely free of any significant side effects of its own.

The ability to rapidly terminate even profound rocuronium-induced blockade (in particular) is a major benefit of sugammadex. In humans, it has been widely used when the anaesthetist has administered rocuronium to facilitate endotracheal intubation but has been subsequently unable to visualize the larynx or pass an endotracheal tube. In this situation, the patient is paralysed and therefore apnoeic, but the anaesthetist may be unable to provide manual ventilation. A number of case reports exist in the human literature of patients being 'rescued' from this 'can't intubate/can't ventilate' scenario by administration of sugammadex, as this agent permits rapid restoration of neuromuscular transmission and spontaneous ventilation. The role of sugammadex as an NMBA reversal agent in other situations is less clearly defined, principally because the drug is extremely expensive; thus, its use can be justified where the patient's life may be at risk, but not for 'routine' situations. Although antagonism of NMBAs using sugammadex has been reported in animals, its high price is likely to dramatically limit its use in veterinary anaesthesia.

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