Practical Pharmacology of Neuromuscular Blockade

Blair Munford, BMedSci, MB, ChB, FANZCA[1]

[1] NRMA Careflight/NSW Medical Retrieval Service, Westmead (NSW), Australia

Address for correspondence and reprints:
Blair Munford, BMedSci, MB, ChB, FANZCA,
NRMA Careflight/NSW Medical Retrieval
Service, P.O. Box 159, Westmead (NSW),
Australia 2145

1067-991X/98/$5.00 + 0

Reprint no. 74/1/93545

Introduction

In the past 10 years, the use of neuromuscular blocking agents, also known as paralytics or muscle relaxants, has gone from limited use by physician-staffed air medical programs to widespread use by flight nurses and flight paramedics. Yet many who use these drugs may not possess the wide knowledge of their pharmacology that perhaps they should. The purpose of this article is to provide a pragmatic guide to the practice and pitfalls of using these agents without overwhelming the reader with an avalanche of molecular biology and pharmacokinetic models.

A word on terminology: the term *muscle relaxant* is somewhat ambiguous because it encompasses not only the neuromuscular blockers (NMBs) that are the subject of this article but also a variety of agents that reduce muscle tone by central mechanisms, such as benzodiazepines, anticholinergics (eg, orphenadrine), and the peripherally acting agent dantrolene. The term *paralytic* is less ambiguous but is not widely used outside North America. The most accurate generic term for drugs that reduce skeletal muscle tone by interfering with neuromuscular transmission is *NMBs*.

Rationale for Using Muscle Relaxants

NMBs are used for a variety of reasons:

- To produce sufficient paralysis to permit surgical or other procedures (eg, endotracheal intubation)
- To permit various modes of ventilatory support without interference from spontaneous respiratory efforts
- To lower airway pressures during respiratory support by increasing chest wall compliance
- To reduce oxygen consumption during critical illness

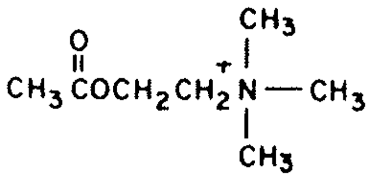
Obviously not all patients require muscle relaxants to achieve these aims. The cardiac arrest patient as a rule can be intubated without relaxants because of the reduction in muscle tone from central nervous system (CNS) hypoxia. The patient obtunded from a sedative or narcotic overdose is often similarly hypotonic as a result of reduced CNS efferent activity.

So why do we use muscle relaxants at all? Why not just higher doses of sedatives? The reason is that sedative doses high enough to produce the aims outlined above often are associated with significant side effects, principally cardiovascular effects. This spur led to the development of muscle relaxants for use in anaesthesia—the concept of balanced anaesthesia with hypnosis, analgesia, and atonia/areflexia provided by a blend of drugs rather than relying on deep inhalational anaesthesia to provide all of these. Also, sedative agents tend to have higher volumes of distribution and hence longer elimination half-lives and are more difficult to reverse than NMBs.

Neuromuscular Physiology

NMBs act at the myoneural junction

Figure 1 **Acetylcholine Structure**



$\mathrm{CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{+}{N}(CH_3)_3}$

formed when the axon of a motor neuron loses its myelin sheath and divides into a number of end feet or terminal buttons. These fit into corresponding depressions on the cell membrane of one or more skeletal muscle fibers. These depressions are called motor end-plates. The nerve cell, together with the muscle fibers it innervates, is called the motor unit. The terminal button of the axon is responsible for synthesizing and releasing the neurotransmitter acetylcholine (ACh). Figure 1 illustrates the ACh structure.

The terminal buttons are separated from the end-plates of the muscle fibers by a narrow gap, called the synaptic cleft, that is 20 to 50 nm wide (0.02 to 0.05 mm). The motor end-plate is a specialized portion of the membrane of the muscle fiber that contains ACh receptors.

Neuromuscular transmission begins with the arrival of an action potential at the unmyelinated terminal portion of the motor neuron. The action potential can be viewed as a wave of current, reversing and then restoring the normal (resting) cell membrane potential of the axon, which is around 90 mV (inside the cell being negative). The reversal is caused by an influx of sodium (Na+) ions through proteins known as sodium channels or gates, and the potential change caused by this influx opens adjacent sodium gates, thereby propagating the wave down the axon. Restoration then is caused by an inward flux of potassium (K+) ions, which restores the -90 mV potential and closes the sodium gates. Action potentials in motor axons, like sensory axons, can be blocked by local anesthetic agents, such as lidocaine.

The arrival of the action potential triggers the release of multiple small packets or quanta of ACh from vesicles in the terminal buttons. The magnitude of this release is proportional to the serum Ca 2+ level and inversely proportional to serum Mg 2+ and is postulated to involve cyclic AMP. The ACh binds to nicotinic cholinergic receptors on the motor end-plate, causing a change in membrane permeability to ions. This change in permeability causes a decline in the trans membrane potential from approximately -90 to -45 mV (threshold potential). At that point, an action potential is propagated over the cell membrane of the skeletal muscle fiber or sarcolemma.

Postjunctional cholinergic receptors are glycoproteins. Each consists of five subunits designated alpha through delta. Two alpha subunits are the binding sites for ACh. In close proximity to these receptors is acetylcholinesterase, an enzyme responsible for the rapid hydrolysis (less than 15 milliseconds) of ACh to acetic acid and choline. This rapid hydrolysis of ACh prevents sustained depolarization of the neuromuscular junction. Choline can reenter motor nerve endings to become substrate in the synthesis of new ACh. Extrajunctional cholinergic receptors exist on skeletal muscle fibers and proliferate in situations in which stimulation of the skeletal muscle by the nerve is deficient.

The process by which depolarization of the sarcolemma initiates mechanical muscle activity is described as excitation-contraction coupling. The action potential is transmitted deep into skeletal muscle along functional infoldings of the sarcolemma known as transverse (T) tubules. The T tubule action potentials in turn cause the sarcoplasmic reticulum (SR) to release stored Ca 2+ in the immediate vicinity of all myofibrils. The Ca 2+ ions are the "final messenger," binding to the muscle protein troponin and abolishing its inhibitory effect on the reaction between myosin and actin.

The activated head of a myosin molecule links to an actin molecule (cross-bridging), producing movement that is repeated in serial fashion to contract the muscle fiber. Each interaction of myosin with actin requires hydrolysis of adenosine triphosphate (ATP) to the diphosphate (ADP). ATP also provides the energy for Ca 2+ reuptake by the SR. Lowering of the Ca 2+ halts cross-bridging between myosin and actin, and the muscle relaxes. Failure of this Ca 2+ pump is the etiology of malignant hyperthermia.

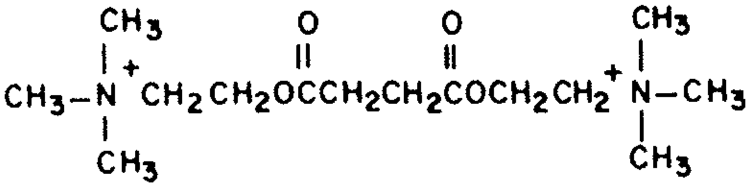
Principles of Neuromuscular Pharmacology

NMBs function by binding to the ACh sites on the alpha subunits of postjunctional cholinergic receptors. To do this, they obviously must partially mimic the three-dimensional structure of ACh. The important portion of the structure appears to be the quaternary nitrogen (any positively charged nitrogen atom bonded to four hydrocarbon chains). As a rule drugs that have neuromuscular-blocking activity have two quaternary nitrogens or at least two groups that can become or act like quaternary nitrogens. From this rule we can deduce some important practical points about the pharmacodynamics and pharmacokinetics of NMBs.

First, NMBs are highly polar molecules with minimal lipid solubility; hence they will distribute only into the extracellular fluid volume, with some binding to plasma proteins (variable from drug to drug). This fact means that dosages of NMBs as a rule should be calculated on patients' lean or ideal body weight (IBW) rather than on their actual weight in the case of morbidly obese patients. The low lipid solubility also means these drugs will tend not to cross either the blood brain barrier or the placenta (the latter being an important point in general anaesthesia for Cesarean section, for example).

Second, drugs that resemble ACh can be expected to have some activity at other cholinergic receptors, which are widespread, especially in the autonomic nervous system. The first stage or preganglionic neurotransmitter in both the sympathetic and parasympathetic divisions of the autonomic nervous system is ACh, and the receptors have some similarity to the motor end-plate in that both are sensitive to nicotine. However, they are not identical in that some drugs act on one or the other but not both. The motor end-plate is classified as type N1, and ACh receptors in autonomic ganglia are type N2. ACh is also the postganglionic or second stage neurotransmitter in the parasympathetic division. Here the receptors are a different type known as muscarinic. In particular, the earlier

Figure 2 **Succinylcholine Structure**



$$\mathrm{CH_3-\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}CH_2CH_2O\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}-CH_3}$$

NMBs are what I would describe as "dirty" drugs, which have widespread effects on ACh receptors, including N2 and muscarinic types. This must be taken into account when selecting an NMB.

Third, as nitrogen-containing bases, many nondepolarizing muscle relaxants (NDMRs) have histamine-releasing actions. This ability is shared by many other agents, such as morphine.

Fourth, agents that decrease muscle tone can be expected to decrease ATP use and hence O_2 consumption and CO_2 production, as well as heat production, although depolarizing relaxants actually produce a transient rise in all of these. The role of muscle relaxants in hypothermia during air medical transport has been addressed,[1,2] although these studies were not controlled for other factors like severity of illness or injury.

Another point worth noting is that sedatives, especially in high doses, also are associated with all of the above, including hypothermia, so avoiding NMBs may not solve the problem if higher doses of sedatives are the alternative.

Classification of NMBs

NMBs may be divided into two major categories, depolarizing and nondepolarizing, depending on the way they act at the receptor. This action in turn relates to their structure. Depolarizing relaxants, of which succinylcholine is the only drug in current use, have their two quaternary nitrogens joined by a flexible carbon chain. They work by imitating ACh and activating the postsynaptic receptor to produce depolarization. Unlike physiological depolarization by ACh, however, depolarization by succinylcholine persists and maintains the muscle fiber in its relaxed state. In contrast, NDMRs have more rigid aromatic (incorporating one or more hydrocarbon rings) structures separating the quaternary (or quaternary equivalent) nitrogens, 1 to 1.25 Angstroms (0.1 to 0.125 nm) apart. NDMRs bind to the receptor without activating it.

The difference between the two NMB types can be illustrated by an analogy. Consider a muscle fiber to be a loaded gun. If I have a loaded firearm, I can make it safe in one of two ways: I can apply the safety catch, thereby impeding the normal trigger mechanism. This method is analogous to an NDMR. Alternatively (perhaps I don't know where the safety catch is), I can fire the weapon and then not reload it (this example assumes the gun is not a semiautomatic!), which is analogous to using succinylcholine. The analogy extends further: firing the weapon—using succinylcholine—in itself may cause some problems or undesirable consequences.

Pharmacology of Succinylcholine

Despite the long list of side effects, succinyldicholine, usually known as succinylcholine (Scoline or Anectine), still remains a useful NMB to facilitate tracheal intubation because of its rapid onset and short duration of action. The structure of succinylcholine, shown in Figure 2, is basically two ACh molecules "back to back." It comes as a solution of 50 mg/mL of the chloride salt. Because succinylcholine slowly hydrolyses at room temperature, it should be refrigerated for storage but can be kept safely for several days to several weeks at normal room temperature before degradation becomes significant.

Neuromuscular effects. Although as little as 0.3 mg/kg may produce significant blockade, the usual intravenous dose is 1 to 1.5 mg/kg (of IBW), which produces rapid onset of action. If precurarization is used, the dose rises to 2 mg/kg, and when intravenous access is unobtainable, intramuscular doses of 4 mg/kg have been used in pediatrics. Although much of the dose is hydrolysed in the plasma by the enzyme pseudocholinesterase before reaching the motor end-plate, the portion that does make it produces the characteristic muscle fasciculations of depolarizing block, followed by flaccid paralysis.

The description of succinylcholine's action is probably an oversimplification because some of the effects may be a result of action on presynaptic and extrajunctional ACh receptors also. In a normal situation, offset of succinylcholine effect is rapid because of continuing hydrolysis by pseudocholinesterase into succinylmonocholine, then succinic acid and choline. Succinylmonocholine has weak neuromuscular-blocking and some other ACh-like actions.

Other neuromuscular effects may be seen. Some muscles, notably the masseter muscles of the jaw, may exhibit a sustained increase in tension. This tension is probably more prevalent in pediatric populations in which it may be clinically apparent as poor intubating conditions in up to 5% of patients. Large or repeated doses of succinylcholine will give rise to a Phase II block ("dual block") that exhibits features of nondepolarizing blockade, such as fade and antagonism by anticholinesterases. Phase II block is prolonged, unpredictable, and exhibits tachyphylaxis (increasing doses are required to maintain the same endpoint). For this reason, the use of repeat succinylcholine doses or infusions have been rendered obsolete by the newer, shorter-acting NDMR agents.

Side effects. Because of its structural relationship to ACh, succinylcholine can be expected to exhibit some parasympathetic activity, but this tendency is infrequent with a single dose. Because succinylcholine also increases the release of catecholamines (for which the mechanism is unknown), this may mask ACh-like actions. Bradycardia is more likely to be seen with a second dose (and in children), responds to anticholinergic agents

Table 1 Properties of Nondepolarizing Muscle Relaxants

Drug	Dose (mg/kg)	T onset (min)	T1[†] (min)	T2[†] (min)	Histamine release	Heart rate change	Blood pressure change	D1* (renal)	D2* (hepatic)
Atracurium	0.5-0.7	3-5	10-15	25-30	+	0/+	0/-	0	0
Cisatracurium	0.1	4-6	10-15	25-30	-	0	0	0	0
d-Tubocurarine	0.5	4-6	30-35	70-90	++	+ or -	—	+	++
Mivacurium	0.1+0.1[*]	2-3	8-12	12-20	+ to ++	0/+	0 to —	0	0
Pancuronium	0.08-0.1	4-5	25-40	60-90	-	++	++	++	+
Rocuronium	0.6	1-2	10-15	20-25	-	0/+	0/+	+	++
Vecuronium	0.08-0.1	3-5	10-15	20-25	-	0/-	0	+	++

NOTES:

[†] T1: interval until recovery wears off and reversal with anticholinesterases can be given; T2: time to complete recovery

* D1: Prolongation of duration of effect in patient with renal impairment; D2: prolongation of duration in patient with hepatic impairment

[*] Mivacurium given in divided dose or slowly over 1 min

(eg, atropine and glycopyrrolate), and may be partly a result of succinylmonocholine.

The fasciculations almost always seen with depolarizing blockade have a number of undesirable effects apart from simply myalgia. Intragastric pressure increases as a result of abdominal muscle fasciculation and may predispose regurgitation and aspiration. For this reason, cricoid pressure is recommended to accompany all succinylcholine administrations. Fasciculations also may contribute to a rise in intracranial pressure (ICP) by increasing venous return and also intrathoracic pressure, both of which will raise central venous pressure (CVP) and hence dural venous sinus pressure and CVP. In addition, the transient increase in CO_2 production also may contribute to elevated ICP.

Fasciculations may be abolished or reduced by the prior administration of a small dose of an NDMR, which is referred to as precurarization. The literature is confusing in this regard because d-tubocurarine (0.05 mg/kg) is the only drug invariably reported as effective. Varying results are reported for other relaxants, which may relate partly to non-equipotent doses. Probably one-tenth to one-eighth of an intubating dose of any NDMR will be at least partially effective, provided it is given 3 to 5 minutes before succinylcholine (more than this amount is likely to produce clinical partial nondepolarizing block). The latter may limit the practicality of precurarization for truly emergent intubation but remains a valuable technique when time is available. If used, the dose of succinylcholine should be increased to 2 mg/kg IBW.

Although both ICP and intraocular pressure increase with succinylcholine (a situation not completely abolished by precurarization nor pretreatment with lignocaine 1 to 1.5 mg/kg), providers should bear in mind that the rise in both pressures may be even greater if intubation is attempted with inadequate sedation and/or nondepolarizing blockade. Both also may rise if the airway is not secured and hypoxia supervenes. Hence succinylcholine should be regarded as relatively rather than absolutely contraindicated in the patient with open eye injury or intracranial hypertension.

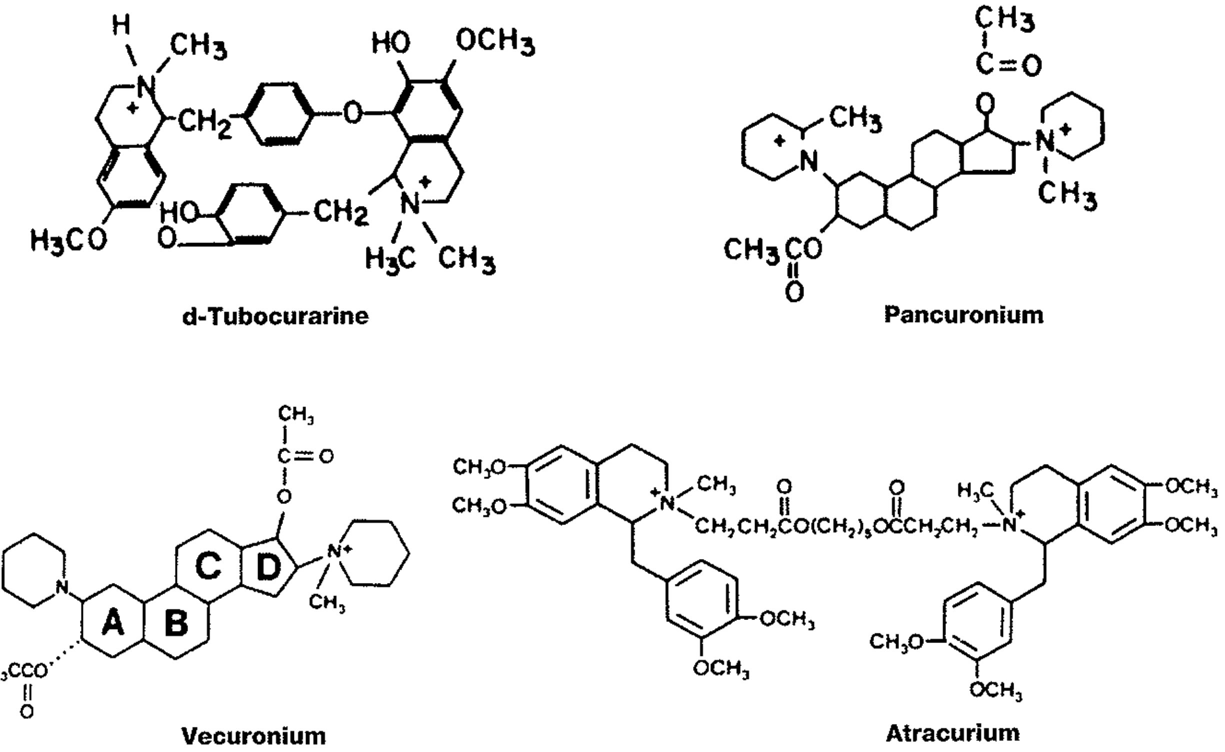
Serum potassium (K+) increases up to 1 mmol/L in the normal patient after succinylcholine injection, and again this increase is not fully prevented by precurarisation. Preexisting hyperkalemia does not exacerbate this situation but may result in the final level being in the danger zone. However, because the rate of change rather than the absolute level of K+ is the critical factor, this possibility is unlikely to be a problem unless the preexisting hyperkalemia itself is of sudden onset.

Of more concern and potentially leading to cardiac arrest is the much larger rise in K+ that may occur when succinylcholine is given to the patient with denervated muscle. Muscle denervation, which may be anatomical or functional, rapidly results in a proliferation of extrajunctional ACh receptors, rendering the patient exquisitely sensitive to succinylcholine. A wide variety of causes can produce these changes: spinal cord injury, head injury, burns, cerebrovascular accident, demyelinating or degenerative CNS disorders, or even prolonged immobility. Normally a "window" of 6 to 12 hours from the acute onset of such disorders is available in which administering succinylcholine safely is possible.

However, hyperkalemia of similar magnitude also may occur in patients with burns or crush injuries by a more direct mechanism: liberation of K+ directly from damaged muscle fibers. The window does not exist in this situation. The risk versus gain of using succinylcholine in patients with muscle denervation or damage should be carefully evaluated. Succinylcholine should not be given in this scenario without ECG monitoring and the availability of drugs, such as dextrose or insulin, bicarbonate, and calcium, to treat rises in serum K+, including hyperkalemic arrest.

As the offset of succinylcholine action depends on hydrolysis by pseudocholinesterase, the duration of block will depend on the level and activity of this process. Some reduction in plasma cholinesterase activity is seen in pregnancy and a variety of disease states, including liver disease, uraemia, and cachexia. Mild prolongation of succinylcholine activity may occur. More serious prolongation occurs in patients who are homozygous for absent or abnormal pseudocholinesterase. Although heterozygotes have mild prolongation only,

Figure 3 Nondepolarizing Muscle Relaxant Structures



d-Tubocurarine

Pancuronium

Vecuronium

Atracurium

the duration of action in homozygotes (1 in 1500 to 2000) may be 3 to 6 hours. Not to be confused with Phase II block, this "scoline apnoea" should not be treated with anticholinesterases. Appropriate treatment is ventilatory support until the succinylcholine wears off; this period may be shortened somewhat by administering blood products, such as fresh frozen plasma that contains pseudocholinesterase.

Succinylcholine does have histamine-releasing activity and also is a recognized trigger of anaphylaxis and/or anaphylactoid reactions. Although succinylcholine is the most common cause of such reactions of all the sedative and paralytic drugs, the occurrence is still low in proportion to its use. In addition, succinylcholine is implicated as a trigger for malignant hyperthermia in susceptible individuals and absolutely is contraindicated in these patients.

Nondepolarizing Muscle Relaxants

Unlike depolarizing blockers, of which only one is significant, a significant number of different NDMRs are in use. These relaxants vary in structure, potency, onset and duration of effect, and cardiovascular and other side effects.[1] Table 1 features NDMR properties; Figure 3 illustrates the structure of NDMRs. All NDMRs act as competitive antagonists to ACh at the motor endplate without any agonist activity. Clinical effects are seen only when more than 70% of receptors are occupied and become maximal at 92% to 95% occupancy.

As a general rule, the more potent agents have a slower onset time if given in equipotent doses. This slower pace is thought to be because the diffusion to the site of action is faster with the greater number of molecules present with the less potent agents. Onset of action of all NDMRs may be accelerated by increasing the dose, but the possibility of doing this may be limited by the cardiovascular side effects or prolonged duration of action. Onset also may be accelerated by using the "priming principle:" giving a small initial amount sufficient to occupy a significant proportion (but less than 70%) of receptors before following with the rest of the dose.

Resistance to NMDRs is seen in patients with burns and starts some hours after injury. It occurs at all sites, not just the injured area. This opposition is thought to occur because of the proliferation of receptors in response to circulatory mediators, such as epinephrine and prostaglandins. Resistance also may occur in sepsis.

The actions of all NMDRs may be reversed by anticholinesterases, such as neostigmine or edrophonium. These drugs increase ACh levels by inhibiting its hydrolysis. Administration of anticholinesterases must be accompanied by a parasympatholytic (antimuscarinic) agent, such as atropine or glycopyrrolate, to counter the parasympathetic side effects of anticholinesterases, such as bradycardia and bronchorrhea.

Specific NDMRs

d-Tubocurarine (dTC). This drug, the first muscle relaxant developed, is a monoquaternary vegetable alkaloid extracted from the curare plant as used by South American Indians as an arrow tip poison. dTC is excreted unchanged in both urine and bile. The usual dose is 0.3 to 0.5 mg/kg. In this dosage, this NDMR has a slow onset and marked cardiovascular side effects related to both ganglionic blockade and histamine release. Because of its cardiovascular effects, prolonged action, and slow onset, dTC seldom is used now, although it still may be the most effective agent for precurarization (0.04 mg/kg). dTC's efficacy and duration are markedly increased by acidosis, reflecting an increase in the bi-ionized proportion. Normally this drug would not be regarded as a good choice for prehospital use or critical care transport.

Metocurine. This semisynthetic methylated derivative of dTC is approximately twice as potent as dTC and causes less histamine release but is otherwise similar. Like dTC, it probably has no place in the prehospital or transport setting.

Pancuronium (Pavulon). This potent agent was the first "designer" NDMR and used a steroid nucleus as the skeleton onto which two quaternary nitrogens were attached just over 1 Angstrom apart. Like dTC, this drug has a slow onset of action at its usual dose (0.08 to 0.1 mg/kg). Elimination is predominantly renal. Pancuronium does not cause histamine release but tends to raise both heart rate and blood pressure because of a combination of noradrenaline release and muscarinic blocking (vagolytic) effects.

The sympathomimetic effects of pancuronium make it an excellent choice for patients in whom heart rate and blood pressure must be maintained, such as severe hypovolemia and high spinal cord injuries. Unlike dTC, this NDMR can be used at higher doses (up to 0.3 mg/kg) to speed onset times. However, this dose is associated with markedly delayed offset. Its established role as the agent of choice in hypotensive patients is being challenged by such newer agents as rocuronium.

A practical disadvantage for use outside the hospital is that pancuronium should be refrigerated for storage. However, it is stable for up to 1 month at room temperature, provided precautions are taken to protect against temperature extremes.

Pipecuronium. This drug is related to pancuronium but has little or no sympathomimetic actions. Onset and offset times are longer than for pancuronium. Pipecuronium is another agent that has been rendered nearly obsolete by shorter-acting cardiostable agents.

Doxacurium. This biquaternary compound is chemically unrelated to other agents but pharmacokinetically is very similar to pancuronium. Pharmacodynamically, this NDMR lacks pancuronium's sympathomimetic actions. Like pipecuronium, it largely has been superseded by vecuronium.

Vecuronium (Norcuron). This monoquaternary derivative of pancuronium has become the standard NDMR in many applications. It is equipotent with pancuronium, and although its elimination half-life is similar, offset of action is faster because of some redistribution. Vecuronium also undergoes hepatic metabolism, with some metabolites having NDMR activity. These factors mean that, after prolonged use, neuromuscular blocking actually may persist longer than pancuronium in the patient with normal renal function.

The literature describes this agent as being devoid of cardiovascular side effects. Although vecuronium certainly lacks the sympathomimetic effects of pancuronium, it has been my experience that it may produce bradycardia, particularly when used in combination with fentanyl and its derivatives. This complication may be seen especially in association with visceral stimuli, including such procedures as urinary catheterization and passage of an intragastric tube, which may be required in air medical transport. Such bradycardia, however, is responsive to atropine. The usual intubation dose of 0.08 mg/kg may be increased or the priming principle used to speed onset of action, but these actions increase the risk of bradycardia and still do not rival either succinylcholine or rocuronium for onset.

Vecuronium is a useful front-line NDMR for prehospital or interhospital use, but the limitations outlined above mean it may not be suitable for every patient. A minor practical disadvantage is that vecuronium is supplied as a powder that is reconstituted with water.

Atracurium (Tracrium). Introduced around the same time as vecuronium, atracurium was the first of an entirely new class of drug: the benzoisoquinolones. Atracurium and its derivatives degrade spontaneously at body temperature and pH by two different mechanisms, meaning the duration of action is independent of both renal and hepatic function and pseudocholinesterase activity. Some atracurium metabolites may have slight neuromuscular-blocking activity, but one—laudanosine—is a CNS stimulant that may precipitate seizures in high dosages. This possibility is extremely unlikely to occur in most clinical scenarios.

Atracurium does release histamine and is relatively contraindicated in asthma and related disorders. At the usual initial dose of 0.5 to 0.6 mg/kg, atracurium is no faster in onset than dTC, pancuronium, or vecuronium, and dosage increase is limited by markedly elevated histamine release at higher doses. Atracurium needs to be stored in a refrigerator and may decompose quite quickly at warmer than room temperature, somewhat limiting its practical application in the prehospital environment.

Cisatracurium (Nimbex). Atracurium is a mixture of 10 isomers of which cisatracurium is one. This NDMR shares most properties with its parent mixture, including spontaneous hydrolysis, but is 4 to 5 times more potent. Cisatracurium's major advantage over atracurium is the absence of histamine release at all clinically used doses; it also produces less laudanosine and other toxic metabolites. The major disadvantage is the onset of action, which, as expected, is markedly slower than less potent atracurium. However, cisatracurium theoretically can be given in much higher doses without hypotension or significant prolongation of action, although this theory has not been fully explored to date in clinical trials. Like atracurium, cisatracurium should be refrigerated.

Rocuronium (Esmeron). This drug is another steroid-based muscle relaxant related to vecuronium and pancuronium but is less potent (approximately one-sixth). This decreased potency results in much more rapid onset than other NMDRs. The duration of action and elimination half-life are similar to vecuronium. Apparently no significant cardiovascular side effects exist to prevent dosage increases, but I have observed occasional mild rises in heart rate. Up to 1.2 mg/kg has been given in some studies; however, these higher doses are associated with markedly prolonged duration of action.

Onset of action has been comparable to succinylcholine in some studies. However, these studies usually have been in under anaesthesia incorporating a volatile anaesthetic agent, such as isoflurane, which both contributes to neuromuscular blocking and masks any incomplete block. Rocuronium's onset of action compared with succinylcholine is likely to be less favorable in the emergent intubation when given on a background of, for example, solely midazolam (Versed). Nonetheless, in my opinion, rocuronium is likely to become the "gold standard" NDMR, especially in the air medical setting. It is certainly the first choice NDMR for intubation, a procedure for which succinylcholine is contraindicated.

Mivacurium (Mivacron). This relatively new NDMR is hydrolysed by plasma cholinesterase. Its advantages are principally a short duration (for NMDRs) of action (under 30 minutes to full recovery without reversing agents). Its disadvantages are significant histamine release and relatively slow onset of action; the former prevents increasing the dose markedly to overcome the latter. Histamine release may be minimized by slow administration (divided doses or slow constant administration over 60 seconds), but this option obviously limits the drug's value in the emergency situation. A further potential hazard is that, like succinylcholine, mivacurium's prolonged action will be seen in patients with pseudocholinesterase deficiency. The prolonged action of mivacurium with the reduced pseudocholinesterase activity seen in liver disease appears to be greater than that of succinylcholine.

Monitoring Neuromuscular Blocking

As with all patient monitoring, clinical observation is the cornerstone of monitoring neuromuscular blockade. Gagging, hiccoughing, or swallowing obviously indicate incomplete neuromuscular blockade. Incomplete blockade also may be indicated by such monitoring modes as capnography, in which the trace may show the patient's own respiratory efforts interspersed with ventilator breaths, or airway pressure manometry, in which a rise in airway pressures may indicate decreasing chest wall or diaphragmatic compliance.

Specific monitoring of neuromuscular blockade may be done with a nerve stimulator. Electrodes are placed over a peripheral nerve (often the ulnar nerve at the wrist), and the response of muscle enervated by that nerve (adductor pollicus in the thenar eminence) is observed or measured. The stimulus commonly used is a series of four current pulses of 40 to 80 milliamperes (train of four). Nondepolarizing blockade (unless absolutely total) will show decreasing response to each successive twitch (fade). This response is a result of recurrent stimuli producing successively smaller amounts of ACh to compete with the NDMR at the motor end-plate.

By comparison, depolarizing blockade is characterized by no fade but shows equal depression of all four twitches. With nondepolarizing blockade, the presence of only one or two visible or palpable twitches of four usually signifies adequate muscle relaxation of the abdominal and chest wall musculature and diaphragm. Nondepolarizing blockade also exhibits an enhanced response to a train of four shortly after a sustained 50 Hz stimulation (tetanus) of the nerve, which persists for 1 to 2 minutes. This test is known as posttetanic facilitation and can be used to monitor the progress of very deep nondepolarizing blockade in which no twitches are seen with a standard train of four.

Another important aspect of neuromuscular blockade monitoring is to "be aware of awareness." *Awareness*, an anaesthetic term that refers to the patient who is paralyzed but conscious, is a possibility whenever neuromuscular blockade is used. This condition is certainly possible in such air medical scenarios as the patient who is ventilated after a hypoxic episode but then has return of cerebral function while paralyzed and ventilated.

As a general rule, NMBs should be administered only in conjunction with adequate doses of sedative and/or narcotic agents. Some published regimens for NDMRs that use minimal doses of sedatives are likely to produce a significant incidence of awareness.[3,4] Even then the possibility of awareness exists because of individual variability of response to these agents. Signs of awareness are principally those of increased sympathetic outflow, including tachycardia, hypertension, perspiration, and lacrimation. Some of these signs may be masked by other agents, such as beta-blockers or calcium antagonists. The best solution is to be alert to the possibility of awareness and avoid wherever possible the combination of deep neuromuscular blockade and light sedation.

Interactions of NMBs

A significant number of drugs either interfere with or potentiate the actions of NMBs. Drugs that potentiate neuromuscular blockade by NMBs include:

- Volatile anesthetic agents, such as halothane and isoflurane, probably by a variety of mechanisms
- Local anesthetic agents and other membrane stabilizers, such as quinidine, by affecting prejunctional and/or postjunctional membranes
- Calcium entry blocking drugs, such as verapamil, that interfere with neuromuscular transmission
- Several antibiotics that have NMB-like actions and potentiate both depolarizing and nondepolarizing blockade, including the aminoglycosides (whose action is potentiated by Mg 2+ and antagonised by Ca 2+). Polymyxins and lincosamides also have NMB actions but are not antagonised by Ca 2+.
- Magnesium. NMBs should be used with caution in certain patients (eg, preeclamptic) on Mg 2+ infusions.

Other considerations:

- Depolarizing and nondepolarizing drugs antagonize each other's actions to some extent, as outlined above.
- Drugs, such as aminophylline, that stimulate formation of cyclic AMP facilitate neuromuscular transmission and may interfere with neuro-

muscular blockade.

- Resistance to NDMR action has been seen in patients receiving phenytoin (Dilantin).
- Resistance to NMBs may be seen in patients on calcium.
- Response to NMBs may be unpredictable in patients receiving diuretics as a result of electrolyte changes.

In the presence of the above agents, or if providers are in doubt, neuromuscular blockade should be monitored closely, ideally by nerve stimulator.

Conclusion

Neuromuscular-blocking agents have had an increasing role in air medical transport during the past decade. They are not without problems, however, and may be hazardous when used by providers with inadequate skills, such as failing to intubate after using an NDMR, or knowledge, such as not realizing hyperkalemic arrest may occur after succinylcholine use in a patient with crush injury syndrome. The problem of awareness also must be considered. Nonetheless, these drugs remain useful agents to assist in airway control and ventilation.

The ideal neuromuscular-blocking agent for air medical transport should have these properties:

- Nondepolarization
- Rapid onset (within 30 seconds)
- Short duration of action and immediate reversibility by anticholinesterases
- Offset of action independent of renal or hepatic function
- No cardiovascular side effects or histamine release
- No active metabolites
- Predictable kinetics for infusion
- No mixing required
- Stability when stored at room temperature

None of the currently available agents meets all these criteria, although rocuronium comes closer than most. Although succinylcholine may not be an ideal agent, it still has a useful role. In addition, atracurium, cisatracurium, or mivacurium may be a better choice than rocuronium for use by constant infusion.

Protocols or guidelines for the use of NMBs in air medical transport should allow flexibility to enable the best agent for a given situation to be used. They also should ensure adequate adjuvant sedation is given and include an algorithm for airway control in the event of failed intubation in the paralyzed patient.

References

1. Semonin-Holleran R, Purcell, P, Johnson D, Davis K, Storer D. Neuromuscular blockade and intubation: association with hypothermia in the air medical trauma patient. Air Medical J 1994;13:483-5.
2. Fiege A, Rutherford WF, Nelson DR. Factors influencing patient thermoregulation in flight. Air Medical J 1996;15:18-23.
3. Rose WD, Anderson LD, Edmond SA. Analysis of intubations: before and after establishment of a rapid sequence intubation protocol for air medical use. Air Medical J 1994;13:475-8.
4. Syverud SA, Borron SW, et al. Prehospital use of neuromuscular blocking agents in a helicopter ambulance program. Ann Emerg Med 1988;17:236-42.

Bibliography

Booij LHDJ. Muscle relaxants. In: Grande CM, et al., editors. Trauma anaesthesia and critical care. St Louis: Mosby/ITACCS; 1993. p. 479-84.

Durbin GC Jr. Neuromuscular blocking agents and sedative drugs: clinical uses and toxic effects in critical care units. Crit Care Clin 1991;7:489-505.

Feldman SA. Neuromuscular transmission and block. In: Scurr C, Feldman SA, Soni N, editors. Scientific foundations of anaesthesia: the basis of intensive care. 4th ed. Chicago: Butterworth-Heinemann/Year Book Medical Publishers; 1990. p. 497-506.

Stoelting RK. Neuromuscular blocking drugs [chapter 8]. In: Stoelting RK, editor. Pharmacology and physiology in anesthetic practice. 2nd ed. (CD-ROM) Hagerstown: Lippincott Raven; 1997.

Wood M. Neuromuscular blocking agents. In: Wood M, Wood JJ, editors. Drugs and anaesthesia: pharmacology for anesthesiologists. 2nd ed. Baltimore: Williams & Wilkins; 1990. p. 271-318.