Neuromuscular Blocking Agents

François Donati

David R. Bevan

Key Points

- **Neuromuscular blocking agents** are used to improve conditions for tracheal intubation, to provide immobility during surgery, and to facilitate mechanical ventilation.
- The main site of action of **neuromuscular blocking agents** (muscle relaxants) is on the nicotinic cholinergic receptor at the endplate of muscle. They also have effects at presynaptic receptors located on the nerve terminal.
- Succinylcholine is a **blocking** agent that produces depolarization at the endplate and binds to extrajunctional receptors. In spite of many side effects, such as hyperkalemia, its rapid offset makes it the drug of choice for rapid sequence induction.
- All other drugs available are nondepolarizing. They compete with acetylcholine for the same binding sites.
- Fade in response to high-frequency stimulation (e.g. train-of-four, 2 Hz for 2 seconds) is a characteristic of nondepolarizing blockade. Train-of-four fade is difficult to evaluate manually or visually during recovery when ratio is >0.4.
- The upper airway is particularly sensitive to the effects of nondepolarizing blockade. Complete recovery does not occur until train-of-four ratio at the adductor pollicis is >0.9.
- Residual paralysis is more frequent with long-duration than intermediate-duration **agents**.
- Reversal with anticholinesterases should be attempted when a certain degree of spontaneous recovery is manifest. Ideally, all four twitches in response to train-of-four stimulation should be visible before reversal is given.
- After injection of the selective binding agent sugammadex, **neuromuscular** transmission is restored because of 1:1 binding of sugammadex to rocuronium.

It appears paradoxical that drugs having peripheral effects on **neuromuscular** transmission might have a role in anesthesia. If the patient is anesthetized, why provide **agents** to prevent movement? Yet, the introduction of muscle relaxants, more appropriately called ***neuromuscular blocking agents***, into clinical practice in 1942 was an important milestone in the history of anesthesia.[1] While the usefulness of the new drugs became apparent, there were doubts regarding patient safety. In 1954, Beecher and Todd[2] claimed that anesthetic mortality increased sixfold when muscle relaxants were used. This situation was probably because of the suboptimal use of mechanical ventilation and reversal drugs,

but other controversies have arisen in recent years for a variety of reasons.

For example, the incidence of awareness appears to be greater when **neuromuscular blocking agents** are used,[3] and some authors recommend restricting the use of these drugs whenever possible, as patient movement might be an indicator of consciousness. However, anesthetics act at the spinal cord level to produce immobility; thus, movement in response to a noxious stimulus indicates inadequate analgesia and does not necessarily mean the patient is conscious.[4] Therefore, awareness does not occur because too much **neuromuscular blocking** agent has been given, but because too little anesthetic is administered.

The controversy regarding **neuromuscular blocking agents** and awareness is complicated by the fact that **neuromuscular** blockade seems to affect the bispectral index (BIS), which is the most widely used measure of unconsciousness.[5] Reductions in BIS have been reported in awake individuals receiving succinylcholine and in mildly sedated patients given mivacurium.

Complete paralysis is not required for the duration of all surgical procedures. However, **neuromuscular blocking agents** were found to make a difference in lower abdominal surgery, where surgical conditions were better in patients receiving vecuronium (Fig. 20-1).[6] In addition to providing immobility and better surgical conditions, **neuromuscular blocking agents** improve intubating conditions. The doses of opioids required for acceptable intubating conditions in the absence of muscle paralysis produce significant hypotension (Fig. 20-2).[7] Providing optimal intubating conditions is not a trivial objective. Poor intubating conditions may increase the incidence of laryngeal injury, as manifested by voice hoarseness and vocal cord damage (Fig. 20-3), and the best way to improve intubating conditions is to administer **neuromuscular blocking agents**.[8]

It is also essential to make sure that the effects of **neuromuscular blocking** drugs have worn off or are reversed before the patient regains consciousness. With the introduction of shorter-acting **neuromuscular blocking agents**, many thought that reversal of blockade could be omitted. However, residual paralysis is still a problem, nearly 30 years after if was first described (Table 20-1), and in spite of the availability of shorter-acting **neuromuscular blocking** drugs and widespread use of **neuromuscular** monitoring.[9] Part of this might be related to the recognition that the threshold for complete **neuromuscular** recovery is a train-of-four ratio of 0.9, instead of the traditional 0.7 (Fig. 20-4).[132] Thus, an understanding of the pharmacology of **neuromuscular blocking agents** and reversal drugs is essential.

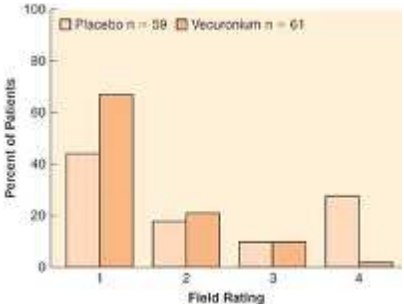

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Figure 20-1. Surgeon's assessment of muscle relaxation during lower abdominal surgery. Rating goes from 1 (excellent) to 4 (poor). The incidence of poor rating was greater in patients not given vecuronium (29%) compared with those who received the drug (2%). (Redrawn from King M, Sujirattanawimol N, Danielson DR, et al: Requirements for muscle relaxants during radical retropubic prostatectomy. Anesthesiology 2000; 93: 1392.)

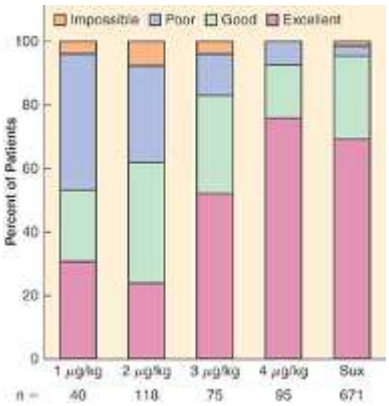

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Figure 20-2. **Neuromuscular blocking agents** provide better intubating conditions than high doses of opioids, without hypotension. Hypnotic agent was propofol or thiopental. Intubating conditions are plotted against dose of remifentanil (in micrograms per kilogram). Results for succinylcholine (Sux), 1 mg/kg (with little opioid) are given for comparison. Hypotension was seen with remifentanil, 4 μg/kg.[7] (Data obtained from several different studies; references 7, 37, 38, 69, 72, 159, and 160.)

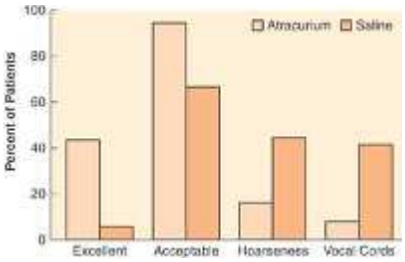

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Figure 20-3. **Neuromuscular blocking agents** improve intubating conditions and reduce vocal cord sequelae. The graph depicts the incidence of excellent and acceptable (defined as good or excellent) intubating conditions after atracurium or saline. The percentage of patients who reported hoarseness and those with vocal cord lesions documented by stroboscopy is also shown. (Data from Mencke et al.[8])

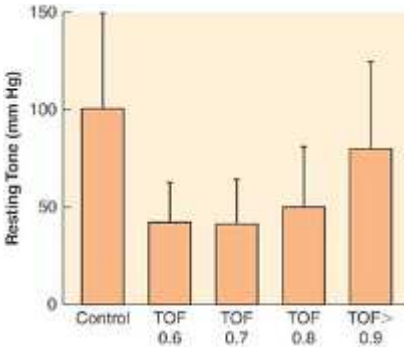

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Figure 20-4. Upper esophageal resting tone in volunteers given vecuronium. Train-of-four ratio (TOF) was measured at the adductor pollicis muscle. Statistically significant decreases compared with control were found at all levels of paralysis until TOF >0.9. (Redrawn from Eriksson LI, Sundman E, Olsson R, et al: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997; 87: 1035.)

Table 20-1 Selected Reports of Residual Paralysis 1979–2007

STUDY	LONG-DURATION DRUGS USED	INTERMEDIATE-DURATION DRUGS USED	REVERSAL	TOF THRESHOLD	RESIDUAL PARALYSIS (% OF PATIENTS)	COMMENTS
Viby-Mogense	*d*-Tubocurarine	—	Yes	0.7	42	—

n et al.,[138] 1979	Pancuronium Gallamine					
Bevan et al.,[163] 1988	Pancuronium		Yes	0.7	36	Less paralysis with
		Atracurium	Yes	0.7	4	atracurium and vecuronium
		Vecuronium	Yes	0.7	9	
Fawcett et al.,[90] 1995		Atracurium/vecuronium bolus	Yes	0.7	12	More paralysis with infusions
		Atracurium/vecuronium infusion	Yes	0.7	24	

Berg et al., 1997 [140]	Pancuronium		Yes	0.7	26	More atelectasis when
		Atracurium/vecuronium	Yes	0.7	5	residual paralysis present
Bissinger et al., [164] 2000	Pancuronium		Yes	0.7	20	More hypoxia with
		Vecuronium	Yes	0.7	8	TOF < 0.7
Gatke et al., [121] 2002		Rocuronium without AMG monitoring	Yes	0.8	17	Less paralysis when AMG used

		Rocuronium with AMG monitoring	Yes	0.8	3	
Debaene et al.,[120] 2003		Atracurium/vecuronium/rocuronium	No	0.7	16	Paralysis could be present even
				0.9	45	4 hr after injection
Murphy et al.,[66] 2003	Pancuronium		No	0.8	82	After cardiac surgery when
		Rocuronium	No	0.8	0	ready to wean from ventilatory support

Murphy et al.,[67] 2004	Pancuronium		Yes	0.7	47	More hypoxia and discharge
				0.9	97	delayed with pancuronium
		Rocuronium	Yes	0.7	7	
				0.9	33	
Baillard et al.,[141] 2005		Atracurium/vecuronium/rocuronium	No (94%)	0.9	63	Less paralysis when reversal and monitoring used
		Atracurium/vecuronium/rocuronium	No (58%	0.9	3	

)

AMG, acceleromyography; TOF, train-of-four ratio.

Physiology and Pharmacology

Structure

The cell bodies of motor neurons supplying skeletal muscle lie in the spinal cord. They receive and integrate information from the central nervous system. This information is carried via an elongated structure, the axon, to distant parts of the body. Each nerve cell supplies many muscle cells (or fibers) a short distance after branching into nerve terminals. The terminal portion of the axon is a specialized structure, the synapse, designed for the production and release of acetylcholine. The synapse is separated from the endplate of the muscle fiber by a narrow gap, called the *synaptic cleft*, which is approximately 50 nm in width (0.05 μm) (Fig. 20-5).[11] The nerve terminal is surrounded by a Schwann cell, and the synaptic cleft has a basement membrane and contains filaments that anchor the nerve terminal to the muscle.

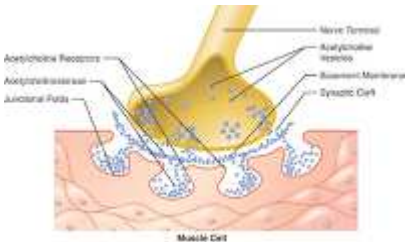

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Figure 20-5. Schematic representation of the neuromuscular junction (not drawn to scale).

The endplate is a specialized portion of the membrane of the muscle fiber where nicotinic acetylcholine receptors are concentrated. During development, multiple connections are made between nerve terminals and a single muscle fiber. However, as maturation continues, most of these connections atrophy and disappear, usually leaving only one connection per muscle fiber. This endplate continues to differentiate from the rest of the muscle fiber. The nerve terminal enlarges, and folds appear. The acetylcholine receptors cluster at the endplate, especially at the crests of the folds, and their density decreases to almost zero in extrajunctional areas.[12] Mammalian endplates usually have an oval shape with the short axis perpendicular to the fiber. The width of the endplate is sometimes as large as the diameter of the fiber, but is usually smaller. However, its length is only a small fraction of that of the fiber.

Nerve Stimulation

Under resting conditions, the electrical potential of the inside of a nerve cell is negative with respect to the outside (typically -90 mV). If this potential is made less negative (depolarization), sodium channels open and allow sodium ions to enter the cell. This influx of positive ions makes the potential inside the membrane positive with respect to the outside. This potential change, in turn, causes depolarization of the next segment of membrane, causing more sodium channels to open, and an electrical impulse, or action potential, propagates. The duration of the action potential is brief (<1 msec) because of rapid inactivation of sodium channels and activation of potassium channels. An action potential also triggers the opening of calcium channels, allowing calcium ions to penetrate the cell. This entry of calcium facilitates release of the neurotransmitter at the nerve terminal.

The sodium channels in the axon may be activated in response to electrical depolarization provided by a nerve stimulator. A peripheral nerve is made up of a large number of axons, each of which responds in an all-or-none fashion to the stimulus applied. Thus, in the absence of **neuromuscular blocking agents**, the relationship between the amplitude of the muscle contraction and current applied is sigmoid. At low currents, the depolarization is insufficient in all axons. As current increases, more and more axons are depolarized to threshold and the strength of the muscle contraction increases. When the stimulating current reaches a certain level, all axons are depolarized to threshold and

propagate an action potential. Increasing current beyond this point does not increase the amplitude of muscle contraction: the stimulation is supramaximal (Fig. 20-6). Most commercially available stimulators deliver impulses lasting 0.1 to 0.2 msec.

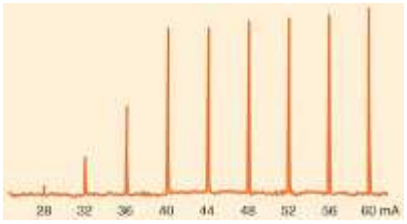

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Figure 20-6. Example of increasing stimulating current in one patient. Current pulses, 0.2-msec duration, were delivered to the ulnar nerve at the wrist every 10 seconds. The force of contraction of the adductor pollicis muscle was measured and appears as spikes. No twitch was seen if the current was <28 mA. At current strengths of ≥40 mA, the current became supramaximal; increasing the current produced little change in force.

Release of Acetylcholine

Acetylcholine is synthesized from choline and acetate and packaged into 45-nm vesicles. Each vesicle contains 5,000 to 10,000 acetylcholine molecules. Some of these vesicles cluster near the cell membrane opposite the crests of the junctional folds of the endplate, in areas called *active zones* (Fig. 20-5).[12] It is now widely accepted that acetylcholine is released in packets, or quanta, and that a quantum represents the contents of one vesicle. In the absence of nerve stimulation, quanta are released spontaneously, at random, and this is seen as small depolarizations of the endplate (miniature endplate potential). When an action potential invades the nerve terminal, approximately 200 to 400 quanta are released simultaneously, unloading approximately 1 to 4 million acetylcholine molecules into the synaptic cleft.[11] Calcium, which enters the nerve terminal through channels that open in response to depolarization, is required for vesicle fusion and release. Calcium channels are located near docking proteins, and this special geometric arrangement provides high intracellular concentrations of calcium to allow binding of specialized proteins on the vesicle membrane with docking proteins.[12] Binding produces fusion of the membranes and release of acetylcholine ensues. When the calcium concentration is decreased, or if the action of calcium is antagonized by magnesium, the release process is inhibited and transmission failure may occur. Other proteins regulate storage and mobilization of acetylcholine vesicles. It appears that a small proportion of vesicles is immediately releasable, while a much larger reserve pool can be mobilized more slowly. Each impulse releases 0.2 to 0.5% of the 75,000 to 100,000 vesicles in the nerve terminal. With repetitive stimulation, the amount of acetylcholine released decreases rapidly because only a small fraction of the vesicles is in a position to be released immediately. To sustain release during high-frequency stimulation, vesicles must be mobilized from the reserve pool.

Postsynaptic Events

The 1 to 10 million receptors located at the endplate bind to acetylcholine as the physiological ligand, and belong to the class of nicotinic receptors. Cholinergic nicotinic receptors respond to acetylcholine

and other agonists by allowing passage of ions. Nicotinic receptors are made up of five glycoprotein subunits arranged in the form of a rosette and lying across the whole cell membrane (Fig. 20-7). The nicotinic subtype present at the **neuromuscular** junction is made up of two identical subunits, designated α, and three others, called ß, δ, and γ or ε. There are two acetylcholine binding sites, each located on the outside part of the α subunit. When two acetylcholine molecules bind simultaneously to each binding site, an opening is created in the center of the rosette, allowing sodium ions to enter the cell and potassium ions to exit.[11,12] The inward movement of sodium is predominant because it is attracted by the negative voltage of the inside of the cell. This movement of sodium depolarizes the endplate; that is, its inside becomes less negative. There is a high density of sodium channels in the folds of synaptic clefts and in the perijunctional area.[12,13] These channels open when the membrane is depolarized beyond a critical point, allowing more sodium to enter the cell and producing further depolarization. This depolarization generates an action potential, which propagates by activation of sodium channels along the whole length of the muscle fiber. The muscle action potential has a duration of 5 to 15 msec and can be recorded as an electromyogram (EMG). It precedes the onset of contraction, or twitch, which lasts 100 to 200 msec. With high-frequency (>10 Hz) stimulation, the muscle fiber does not have time to relax before the next impulse, so contractions fuse and add up, and a tetanus is obtained.

There are two types of nicotinic acetylcholine receptors. Early in development, receptors are evenly distributed along the whole length of the muscle fiber. These receptors, called *fetal* receptors, have a γ subunit (Fig. 20-7). When the endplate develops, receptors tend to cluster at the **neuromuscular** junction and leave only few receptors in the extrajunctional areas. As maturation continues, the γ subunit is substituted by an ε subunit, which is characteristic of the *adult* type, junctional receptor.[12] In humans, the switch occurs in the third trimester of pregnancy. Maintenance of adult receptors at the endplate depends on the integrity of nerve supply. A few γ-type, extrajunctional receptors still persist in adults and can proliferate in cases of denervation. Both types of receptor have

two binding sites for acetylcholine, located on each of the α subunits, but they have slightly different sensitivities to agonist and antagonist drugs.[12]

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Figure 20-7. There are two types of nicotinic receptors in muscle. Both have the same five subunits, except for a substitution of the ε for the γ subunits. The acetylcholine binding sites are represented by a shaded oval area. They are on the α subunit, at the δ and ε or γ interface, respectively. According to some authors, the order of the ß and δ is inverted.

The main action of nondepolarizing **neuromuscular blocking** drugs is to bind to at least one of the two α subunits of the postsynaptic receptor. This prevents access to the receptor by acetylcholine and does not produce opening of the receptor. Under normal circumstances, only a small fraction of available receptors must bind to acetylcholine to produce sufficient depolarization to trigger a muscle contraction. In other words, there is a wide "margin of safety."[13] This redundancy implies that **neuromuscular blocking** drugs must be bound to a large number of receptors before any blockade is detectable. Animal studies suggest that 75% of receptors must be occupied before twitch height decreases in the presence of *d*-tubocurarine, and blockade is complete when 92% of receptors are occupied.[14] The actual number depends on species and type of muscle, and humans might have a reduced margin of safety compared with other species.[13] So it is futile to correlate receptor occupancy data obtained in cats with certain clinical tests in humans, such as hand grip and head lift, which involve different muscle groups. However, the general concept that a large proportion of receptors must be occupied before blockade becomes detectable, and that measurable blockade occurs over a narrow range of receptor occupancy, remains applicable to clinical practice. Because it must overcome the margin of safety, the initial dose of **neuromuscular blocking** agent is greater than maintenance doses.

Acetylcholine is hydrolyzed rapidly by the enzyme acetyl cholinesterase, which is present in the folds of the endplate as well as embedded in the basement membrane of the synaptic cleft. The presence of the enzyme in the synaptic cleft suggests that not all the acetylcholine released reaches the endplate; some is hydrolyzed en route.[12,15]

Presynaptic Events

The release of acetylcholine normally decreases during high-frequency stimulation because the pool of readily releasable acetylcholine becomes depleted faster than it can be replenished. Under normal circumstances, the reduced amount released is well above what is required to produce muscle contraction because of the high margin of safety at the **neuromuscular** junction. In addition, a positive

feedback system involving activation of presynaptic receptors helps in the mobilization of acetylcholine vesicles. Although studies aimed at identifying these receptors are extremely difficult to perform, there is some evidence that there the presynaptic and postsynaptic receptors are of different subtypes. Presynaptic receptors are most likely of the $\alpha_3\beta_2$ subtype, that is they are made up of only α and ß subunits.[16,17] Both the α subunits are slightly different from those found in postsynaptic receptors (thus the designation as α_3, instead of the α_1 given to postsynaptic receptors). The other three subunits are all identical (β_2), and slightly different from the β_1 subunit found in postsynaptic receptors.

The physiological role of the presynaptic receptors is to maintain the number of vesicles ready to be released. Nondepolarizing **neuromuscular blocking** drugs produce characteristic TOF and tetanic fade, probably by **blocking** presynaptic nicotinic receptors,[16] thus preventing mobilization of acetylcholine vesicles and leading to reduced acetylcholine release during high-frequency stimulation. Succinylcholine has virtually no effect on these presynaptic receptors, which would explain the lack of fade observed with this drug.[17] Fade constitutes a key property of nondepolarizing **neuromuscular blocking** drugs and is useful for monitoring purposes.

Neuromuscular Blocking Agents

Neuromuscular blocking drugs interact with the acetylcholine receptor either by depolarizing the endplate (depolarizing **agents**) or by competing with acetylcholine for binding sites (nondepolarizing **agents**). The only depolarizing agent still in use is succinylcholine. All others are of the nondepolarizing type.

Pharmacologic Characteristics of Neuromuscular Blocking Agents

The effect of **neuromuscular blocking** drugs is measured as the depression of adductor muscle contraction (twitch) following electrical stimulation of the ulnar nerve. The value is compared with a control value, obtained before injection of the drug. Each drug has characteristic onset, potency, duration of action, and recovery index.

Potency of each drug is determined by constructing dose-response curves, which describe the relationship between twitch depression and dose (Fig. 20-8).[18] Then, the effective dose 50, or ED_{50}, which is the median dose corresponding to 50% twitch depression, is obtained. Because clinically useful relaxation is attained when twitch is abolished almost completely, the ED_{95}, corresponding to 95% block, is more commonly used. For example, the ED_{95} for vecuronium is 0.05 mg/kg, which means that half the patients will achieve at least 95% block of single twitch (compared with the prevecuronium value) with that dose, and half the subjects will reach <95% block. Rocuronium has an ED_{95} of 0.3 mg/kg. Therefore, it has one-sixth the potency of vecuronium. In other words, compared with vecuronium, 6 times as much rocuronium has to be given to produce the same effect. The ED_{95} of known **neuromuscular blocking agents** vary over two orders of magnitude (Table 20-2).

Onset time, or time to maximum blockade, can be shortened if the dose is increased. When two or more drugs are

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compared, it is meaningful to compare only equipotent doses and usually clinically relevant doses (2 × ED_{95}) are considered.[18]

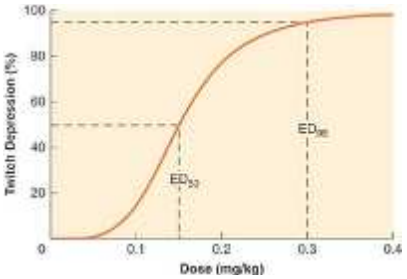

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Figure 20-8. Example of a dose-response relationship. The actual numbers are approximately those for rocuronium. The ED_{50} is the dose corresponding to 50% blockade and ED_{95} is the dose corresponding to 95% blockade.

Duration of action is the time from injection of the neuromuscular blocking agent to return of 25% twitch height (compared with control). Duration increases with dose, so comparisons are normally made with 2 × ED_{95} doses. The 25% twitch height figure was chosen because rapid reversal can normally be achieved at that level. Categories were proposed for neuromuscular blocking drugs according to their duration of action (Table 20-2).[18] Same duration agents may have markedly different onsets.

Table 20-2 Potency, Onset Time, Duration, and Recovery Index of Neuromuscular Blocking Agents[a]

AGENT	ED_{95} (mg/kg)	ONSET TIME (min)	DURATION TO 25% RECOVERY (min)	RECOVERY INDEX (25-75% RECOVERY) (min)
ULTRASHORT-DURATION AGENTS				
Succinylcholine	0.3	1–1.5	6–8	2–4
Gantacurium[b]	0.19	1.7	6–8	2.5
SHORT-DURATION AGENTS				
Mivacurium[c]	0.08	3–4	15–20	7–10
Rapacuronium[c]	0.75	1–1.5	15–25	5–7
INTERMEDIATE-DURATION AGENTS				
Atracurium	0.2–0.25	3–4	35–45	10–15
Cisatracurium	0.05	5–7	35–45	12–15
Rocuronium	0.3	1.5–3	30–40	8–12
Vecuronium	0.05	3–4	35–45	10–15
LONG-DURATION AGENTS				
Alcuronium[c]	0.25	3–5	60–90	30–40

Doxacurium	0.025	5–10	40–120	30–40
d-Tubocurarine[c]	0.5	2–4	60–120	30–45
Gallamine[c]	2	1.5–3	60–120	30–60
Metocurine[c]	0.3	3–5	60–150	40–60
Pancuronium	0.07	2–4	60–120	30–40
Pipecuronium[c]	0.05	3–5	90–130	35–45

[a]Typical values for the average young adult patient. Onset and duration data depend on dose. The values presented are the best estimates available for twice the ED_{95} and are measured at the adductor pollicis muscle with nitrous oxide and no volatile agent. Actual values may vary markedly from one individual to the next, and may be affected by age, other medications, and/or disease states. The categories under which the drugs are classified are somewhat arbitrary.

[b]Being investigated at the time of writing.

[c]No longer used or very limited use in North America.

Recovery index is the time interval between 25% and 75% twitch height. It provides information about the speed of recovery once return of twitch is manifest. Contrary to duration of action, it does not depend heavily on the dose given. The values for ED_{95}, onset time, duration of action, and recovery index depend on which muscle is used to make measurements. For consistency, the adductor pollicis muscle has been retained as the gold standard, not because of its physiological significance but because it is most commonly monitored and data on it are most abundant.

The pharmacologic characteristics of **neuromuscular blocking agents** are completed by an assessment of *intubating conditions*, which do not always parallel twitch height at the adductor pollicis muscle. Intubating conditions depend on paralysis of centrally located muscles, but also on the type and quantity of opioid and hypnotic drugs given for induction of anesthesia. To decrease variability between studies,

criteria to grade intubating conditions as excellent, good, poor, or impossible in a scoring system were adopted by a group of experts who met in Copenhagen in 1994.[19]

Depolarizing Drugs: Succinylcholine

Among drugs that depolarize the endplate, only succinylcholine is still used clinically. In spite of a long list of undesired effects, succinylcholine remains popular because it is the only ultrarapid onset/ultrashort duration neuromuscular blocking drug currently available.

Neuromuscular Effects

The effects of succinylcholine at the neuromuscular junction are not completely understood. The drug depolarizes postsynaptic and extrajunctional receptors. However, when the receptor is in contact with any agonist, including acetylcholine, for a prolonged time it ceases to respond to the agonist. Normally, this desensitization process does not occur with acetylcholine because of its rapid breakdown (<1 msec). However, succinylcholine remains at the endplate for much longer, so desensitization develops after a brief period of activation.[17] Another possible mechanism is the inactivation of sodium channels in the junctional and perijunctional areas, which occurs when the membrane remains depolarized.[17] This inactivation prevents the propagation of the action potential. Both desensitization of the receptor and inactivation of sodium channels might be present together.

Within 1 minute after succinylcholine injection and before paralysis is manifest, some disorganized muscular activity is frequently observed. This phenomenon is called *fasciculation*.

This activity probably reflects the agonist effect of succinylcholine, before desensitization takes place. Small doses of nondepolarizing drugs are effective in reducing the incidence of fasciculations.[20]

Succinylcholine has yet another neuromuscular effect. In some muscles, like the masseter and to a lesser extent the adductor pollicis, a sustained increase in tension that may last for several minutes can be observed. The mechanism of action of this tension change is uncertain but is most likely mediated by acetylcholine receptors because it is blocked by large amounts of nondepolarizing drugs.[21] The increase in masseteric tone, which is probably always present to some degree but greater in some susceptible individuals, may lead to imperfect intubating conditions in a small proportion of patients. Masseter muscle spasm may be an exaggerated form of this response.

Characteristics of Depolarizing Blockade

After injection of succinylcholine, single-twitch height is decreased. However, the response to high-frequency stimulation is sustained: minimal train-of-four and tetanic fade is observed. The block is antagonized by nondepolarizing agents so that the ED_{95} is increased by a factor two if a small dose of nondepolarizing drug is given before.[22] Succinylcholine blockade is potentiated by inhibitors of acetyl cholinesterase, such as neostigmine and edrophonium.[23]

Phase II Block

After administration of 7 to 10 mg/kg, or 30 to 60 minutes of exposure to succinylcholine, train-of-four and tetanic fade become apparent. Neostigmine or edrophonium can antagonize this block, which has been termed *nondepolarizing*, *dual*, or *phase II* block. The onset of phase II block coincides with tachyphylaxis, as more succinylcholine is required for the same effect.

Pharmacology of Succinylcholine

Succinylcholine is rapidly hydrolyzed by plasma cholinesterase (also called *pseudocholinesterase*), with an elimination half-life of <1 minute in patients.[24] Because of the rapid disappearance of succinylcholine from plasma, the maximum effect is reached quickly. Subparalyzing doses (up to 0.3 to 0.5 mg/kg) reach their maximal effect within approximately 1.5 to 2 minutes at the adductor pollicis muscle,[22] and within 1 minute at more central muscles, such as the masseter, the diaphragm, and the laryngeal muscles. With larger doses (1 to 2 mg/kg), abolition of twitch response can be reached even more rapidly.

The mean dose producing 95% blockade (ED_{95}) at the adductor pollicis muscle is 0.30 to 0.35 mg/kg with opioid–nitrous oxide anesthesia.[22] In the absence of nitrous oxide, the ED_{95} is increased to 0.5 mg/kg.[25] These values are doubled if *d*-tubocurarine, 0.05 mg/kg, is given as a defasciculating agent.[22] The time until full recovery is dose-dependent and reaches 10 to 12 minutes after a dose of 1 mg/kg.

Side Effects

Cardiovascular

Sinus bradycardia with nodal or ventricular escape beats (or both) may occur, especially in children, and asystole has been described after a second dose of succinylcholine in both pediatric and adult patients. These effects can be attenuated with atropine or glycopyrrolate.[26] The mechanisms for the cardiovascular side effects of succinylcholine are not known because succinylcholine appears to have little effect of autonomic cholinergic receptors.[17] Succinylcholine increases catecholamine release, and tachycardia is seen frequently.

Anaphylaxis

Succinylcholine has been incriminated as the trigger of allergic reactions more often than any other drug used in anesthesia. Successive studies conducted in France indicate that the number of reported events is decreasing, corresponding to the gradual replacement of succinylcholine by nondepolarizing drugs.[27] The incidence of anaphylactic reactions to succinylcholine is difficult to establish, but is probably of the order of 1:5,000 to 1:10,000.

Fasciculations

The prevalence of fasciculations is high (60 to 90%) after the rapid injection of succinylcholine, especially in muscular adults. Fasciculations are a benign side effect of the drug, but many clinicians prefer to prevent fasciculations. In this respect, a small dose of a nondepolarizing **neuromuscular blocking** drug is given 3 to 5 minutes before succinylcholine is effective.[20] When the drug was available, *d*-tubocurarine 0.05 mg/kg was used for this purpose. Rocuronium is an acceptable alternative, as long as appropriate doses (0.03 to 0.04 mg/kg, or 10% of the ED_{95}) are given.[28] In one study, rocuronium, 0.03 mg/kg,

decreased the incidence of fasciculations from 90 to 10%.[29] A dose of 0.06 mg/kg leads to an unacceptably high incidence of symptoms of neuromuscular weakness, such as blurred vision, heavy eyelids, voice changes, difficulty swallowing, or even dyspnea, in the awake patient.[30] A recent meta-analysis shows that these side effects have been observed frequently in studies of defasciculating doses of neuromuscular blocking agents,[20] but these side effects are most likely related to the high dose given.[28] Atracurium, 0.02 mg/kg, is also effective. Pancuronium, vecuronium, cisatracurium, and mivacurium are not as effective as defasciculants. After these nondepolarizing drugs, the dose of succinylcholine must be increased from 1 mg/kg to 1.5 or even 2 mg/kg because of the antagonism between depolarizing and nondepolarizing drugs.[22] Other drugs, such as diazepam, lidocaine, fentanyl, calcium, vitamin C, magnesium, and dantrolene, have all been used to prevent fasciculations. The results are no better than with nondepolarizing relaxants and they may have undesirable effects of their own. The administration of small (10-mg) doses of succinylcholine 1 minute before the intubating dose, does not appear to be effective[29] and has largely been abandoned.

Muscle Pains

Generalized aches and pains, similar to the myalgia that follows violent exercise, are common 24 to 48 hours after succinylcholine administration. Their incidence is variable (1.5 to 89% of patients receiving succinylcholine) and are more common in young, ambulatory patients.[31] The intensity of muscle pains is not always correlated with the intensity of fasciculations, but the methods that have been shown effective to prevent fasciculations usually prevent muscle pains. For example, a precurarization dose of a nondepolarizing neuromuscular blocking agent is effective. Lidocaine (1 to 1.5 mg/kg), especially in conjunction with precurarization, has also been shown to be of value.[31] Calcium, vitamin C, benzodiazepines, magnesium, and dantrolene have been tried with inconclusive results.[31]

Intragastric Pressure

Succinylcholine increases intragastric pressure, and this effect is blocked by precurarization. However, succinylcholine

causes even greater increases in lower esophageal sphincter pressure. Thus, succinylcholine does not appear to increase the risk of aspiration of gastric contents unless the lower esophageal sphincter is incompetent.

Intraocular Pressure

Intraocular pressure increases by 5 to 15 mm Hg after injection of succinylcholine. The mechanism is unknown but occurs after detachment of extraocular muscle, suggesting an intraocular etiology. Precurarization with a nondepolarizing blocker has little or no effect on this increase. This information has led to the widespread recommendation to avoid succinylcholine in open-eye injuries. However, it must be appreciated that inadequate anesthesia, elevated systemic blood pressure, and insufficient

neuromuscular blockade during laryngoscopy and tracheal intubation might increase intraocular pressure more than succinylcholine. In addition, there is little evidence that the use of succinylcholine has led to blindness or extrusion of eye content.[32]

Intracranial Pressure

Succinylcholine may increase intracranial pressure, and this response is probably diminished by precurarization.[33] Again, laryngoscopy and tracheal intubation with inadequate anesthesia or muscle relaxation are likely to increase intracranial pressure even more than succinylcholine.

Hyperkalemia

Serum potassium increases by approximately 0.5 mEq/L after injection of succinylcholine. This increase is not prevented completely by precurarization. In fact, only large doses of nondepolarizing blockers reliably abolish this effect.[34] Subjects with pre-existing hyperkalemia, such as patients in renal failure, do not have a greater increase in potassium levels, but the absolute level might reach the toxic range. Succinylcholine is safe in normokalemic renal-failure patients.[35] Severe hyperkalemia, occasionally leading to cardiac arrest, has been described in patients after major denervation injuries, spinal cord transection, peripheral denervation, stroke, trauma, extensive burns, and prolonged immobility with disease, and may be related to potassium loss via a proliferation of extrajunctional receptors.[34] Hyperkalemia has been reported with myotonia and muscle dystrophies, and cardiac arrests have been reported in children before the diagnosis of the disease was made.[34] Severe hyperkalemia after succinylcholine resulting in cardiac arrest has also been observed in acidotic hypovolemic patients.

Abnormal Plasma Cholinesterase

Plasma cholinesterase activity can be reduced by a number of endogenous and exogenous causes, such as pregnancy, liver disease, uremia, malnutrition, burns, plasmapheresis, and oral contraceptives. These conditions usually lead to a slight, clinically unimportant increase in the duration of action of succinylcholine.[36] Plasma cholinesterase activity is reduced by some anticholinesterases (e.g., neostigmine) so that the duration of succinylcholine given after neostigmine, but not after edrophonium, is increased.[23]

A small proportion of patients have a genetically determined inability to metabolize succinylcholine. Either plasma cholinesterase is absent or an abnormal form of the enzyme is present. Only patients homozygous for the condition (approximately 1:2,000 individuals) have prolonged paralysis (3 to 6 hours) after usual doses of succinylcholine (1 to 1.5 mg/kg). In heterozygous patients (1:30 cases), the duration of action is only slightly prolonged compared with normal individuals. Traditional methods for identifying plasma cholinesterase phenotype involve measurement of enzyme activity with a substrate and inhibition with dibucaine, fluoride, and chloride. These tests are only capable of identifying some enzyme variants. The complete amino acid sequence of plasma cholinesterase has now been determined using molecular genetics techniques. The cholinesterase gene is located on chromosome 3 at q26,[36] and over 20 mutations in the coding region of the plasma cholinergic gene have been identified. Whole blood or fresh-frozen

plasma can accelerate succinylcholine metabolism in patients with low or absent plasma cholinesterase, but the best course of action is probably mechanical ventilation of the lungs until full recovery of neuromuscular function can be demonstrated. Neostigmine and edrophonium are unpredictable in the reversal of abnormally prolonged succinylcholine blockade and are best avoided.

Clinical Uses

The main indication for succinylcholine is to facilitate tracheal intubation. In adults, a dose of 1.0 mg/kg yields 75 to 80% excellent intubation conditions within 1 to 1.5 minutes after an induction sequence that includes a hypnotic (propofol or thiopental) and a moderate opioid dose.[37,38] The dose must be increased to 1.5 to 2.0 mg/kg if a precurarizing dose of nondepolarizing blocker has been used.[22] Intubating conditions without precurarization are only marginally improved by increasing the dose to 2 mg/kg.[38] Succinylcholine is especially indicated for "rapid sequence induction," when a patient presents with a full stomach and the possibility of aspiration of gastric contents. In this situation, manual ventilation of the lungs is avoided, if possible, to reduce the probability of aspiration because of excessive intragastric pressure caused by gas forced via face mask. Thus, the ideal neuromuscular blocking agent has both a fast onset, to reduce the time between induction and intubation of the airway, and a rapid recovery, to allow return of normal breathing before the patient becomes hypoxic. The duration of action of succinylcholine, given at a dose of 1 mg/kg, is short enough so that in the majority of properly preoxygenated patients resume respiratory efforts (5 to 6 minutes) before hypoxia can be detected.[39] It has been argued that this is valid only in relatively healthy subjects and not in all cases. As a result, a lower dose has been suggested. However, a dose of 0.5 to 0.6 mg/kg results in substantially fewer patients with excellent intubating conditions, and the decrease in duration is modest.[37,38] For maintenance of relaxation, typical infusion rates are approximately 50 to 100 µg/kg/min. However, the availability of short and intermediate nondepolarizing drugs makes succinylcholine infusions obsolete.

Children are slightly more resistant to succinylcholine than adults,[40] and doses of 1 to 2 mg/kg are required to facilitate intubation. In infants, 2 to 3 mg/kg may be required. Precurarization is not necessary in patients younger than 10 years because fasciculations are uncommon in this age group. Bradycardia is common in children unless atropine or glycopyrrolate is given.[26] Succinylcholine, at a dose of 4 mg/kg, is the only effective intramuscular neuromuscular blocking agent in children with difficult intravenous access and provides adequate intubating conditions in about 4 minutes. However, this route of administration should not be the method of choice.[41]

In obese individuals, the dose of succinylcholine, in milligrams per kilogram of actual body weight, is the same as in leaner patients. Calculating the dose per kilogram ideal body weight might lead to underdosing and inadequate intubating conditions.[42] The volume of distribution, expressed per kilogram of actual body weight, of succinylcholine is probably

decreased in obese individuals, but this is compensated by an increase in plasma cholinesterase activity.

Nondepolarizing Drugs

Nondepolarizing **neuromuscular blocking** drugs bind to the postsynaptic receptor in a competitive fashion, by binding to one of the α subunits of the receptor (Fig. 20-7).[12]

Characteristics of Nondepolarizing Blockade

The fade observed in response to high-frequency stimulation (>0.1 Hz) is characteristic of nondepolarizing blockade.[16] With EMG recordings, fade is relatively constant in the range 2 to 50 Hz.[43] Mechanical fade is greater with 100 Hz than with 50 Hz.[44] Tetanic stimulation is followed by posttetanic facilitation, which is an increased response to any stimulation applied soon after the tetanus. The intensity and duration of this effect depend on the frequency and duration of the tetanic stimulation. With a 50-Hz tetanus of 5-second duration, twitch responses have been found to fall within 10% of their pretetanic values in 1 to 2 minutes[45] (Fig. 20-9).

Finally, nondepolarizing blockade can be antagonized with anticholinesterase **agents** such as edrophonium, neostigmine, or pyridostigmine. It is also antagonized by depolarizing **agents** such as succinylcholine provided that the nondepolarizing blockade is intense and that the succinylcholine dose is too small to produce a block of its own.

Pharmacokinetics

As is the case for other drugs used in anesthesia, the *elimination half-life* of **neuromuscular blocking agents** does not always correlate with duration of action because termination of action sometimes depends on redistribution instead of elimination. However, knowledge of the kinetics of the drug helps us understand the behavior of the drug in special situations (prolonged administration, disease of the organs of elimination, and so on).

Several mechanisms can explain the various categories of durations of action listed in Table 20-3:

- All *long-duration* drugs all have a long (1 to 2 hours) elimination half-life and depend on liver and/or kidney function for termination of action.

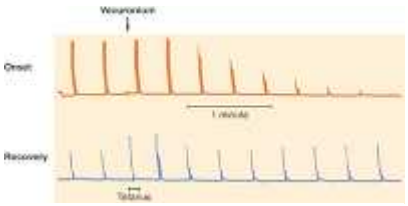

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Figure 20-9. Characteristics of nondepolarizing blockade. Train-of-four responses are equal before administration of vecuronium (*arrow*). For a given twitch depression, fade is less during onset (*top trace*) than recovery (*bottom trace*). A 50-Hz tetanus was applied during recovery. Tetanic fade is seen with posttetanic facilitation, that is a greater train-of-four response after than before the train.

- *Intermediate-duration* drugs either have an intermediate elimination half-life (atracurium and cisatracurium) or they have long elimination half-lives (1 to 2 hours) but depend on redistribution rather than elimination for termination of effect (vecuronium and rocuronium; Fig. 20-10).
- *Short-duration* drugs have either short elimination half-lives (the active isomers of mivacurium) or long elimination half-life but extensive redistribution (rapacuronium).
- *Ultrashort-duration* drugs have a very short elimination half-life (succinylcholine).

The *volume of distribution* of all these **agents** is approximately equal to extracellular fluid (ECF) volume (0.2 to 0.4 L/kg; Table 20-3). In infants, in whom the ECF volume as a proportion of body weight, is increased, the volume of distribution of **neuromuscular blocking** drugs parallels ECF volume closely.

Onset and Duration of Action

Onset time of **neuromuscular blocking** drugs is determined by the time required for drug concentrations at the site of action to reach a critical level, usually that corresponding to 100% block. Onset time (2 to 7 minutes) is longer than time to peak plasma concentrations (<1 minute). This delay reflects the time required for drug transfer between plasma and **neuromuscular** junction and is represented quantitatively by a rate constant (k_{eo}). This rate constant corresponds to half-times of 5 to 10 minutes for most nondepolarizing drugs and is determined by all the factors that modify access of the drug to, and its removal from, the **neuromuscular** junction. These include cardiac output, distance of the muscle from the heart, and muscle blood flow. Thus, onset times are not the same in all muscles because of different blood flows. Also, if metabolism or redistribution is very rapid, for example, in the case of succinylcholine, the onset time is accelerated. Finally, potent drugs have a slower onset of action than less potent **agents** (Fig. 20-11).[46] This is because a large proportion of receptors must be occupied before blockade can be observed. Blockade of these receptors will occur faster, and onset will be more rapid, if

more drug molecules are available, that is, if potency is low. Table 20-2 shows that onset tends to be slower if a drug is potent, that is, if ED_{95} is small.

Duration of action is determined by the time required for drug concentrations at the site of action to decrease below a certain level, usually corresponding to 25% first twitch blockade. Duration is determined chiefly by plasma concentrations, at least for intermediate- and long-duration drugs.

P.508

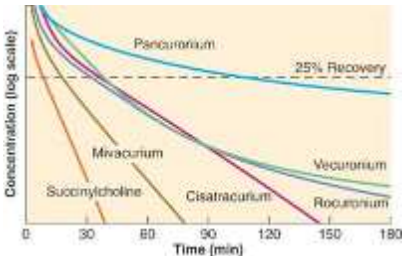

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Figure 20-10. Concentrations at the **neuromuscular** junction for six representative drugs, after bolus doses of 2 × ED_{95}. Concentrations at the **neuromuscular** junction lag somewhat behind plasma concentrations. The level corresponding to 25% recovery is indicated. The curves were moved up or down so that the 25% level matched. Succinylcholine and the active mivacurium isomers have a rapid elimination. Pancuronium has a long half-life and recovery occurs during the elimination phase. Cisatracurium has an intermediate terminal half-life, and recovery also occurs during the elimination phase. Rocuronium and vecuronium have an elimination half-life comparable with that of pancuronium. However, an important redistribution occurs before, and 25% recovery occurs during that redistribution process. As a result, both rocuronium and vecuronium have a duration of action comparable with that of cisatracurium.

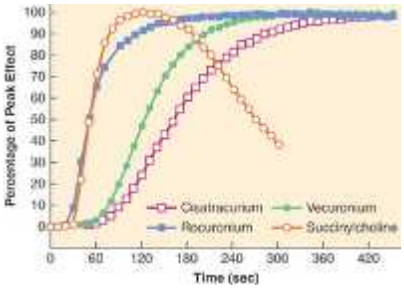

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Figure 20-11. Neuromuscular blockade as a function of time for four neuromuscular blocking agents. Onset is faster for the less potent succinylcholine and rocuronium than for the more potent vecuronium and cisatracurium. (From Kopman AF, Klewicka MM, Kopman DJ, et al: Molar potency is predictive of the speed of onset of neuromuscular block for agents of intermediate, short, and ultrashort duration. Anesthesiology 1999; 90: 425, with permission.)

Table 20-3 Typical Pharmacokinetic Data for Neuromuscular Blocking Agents in Adults, Except where Stated

DRUG	VOLUME OF DISTRIBUTION (L/kg)	CLEARANCE (mL/kg/min)	ELIMINATION HALF-LIFE (min)
ULTRASHORT-DURATION AGENTS			
Succinylcholine	0.04	37	0.65
SHORT-DURATION AGENTS			
Mivacurium			
Trans-trans	0.05	29	2.4
Cis-trans	0.05	46	2.0
Cis-cis	0.18	7	30

Rapacuronium	0.2	7	100
INTERMEDIATE-DURATION AGENTS			
Atracurium	0.14	5.5	20
Cisatracurium			
Adults	0.12	5	23
Intensive care	0.26	6.5	25
Rocuronium			
Adults	0.3	3	90
Intensive care	0.7	3	330
Vecuronium	0.4	5	70
LONG-DURATION AGENTS			
Doxacurium	0.2	2.5	95
d-Tubocurarine			
Adults	0.3	1–3	90
Elderly	0.3	0.8	270

Neonates	0.7	1.1	300
Infants	0.5	1.0	300
Children	0.3	1.5	90
Pancuronium	0.3	1.8	140

Individual Nondepolarizing Agents

Since 1942, nearly 50 nondepolarizing **neuromuscular blocking agents** have been introduced into clinical anesthesia. This section covers only those drugs currently available in North America and Europe, plus a few others of historical interest. The first agent to undergo clinical investigation was Intocostrin, or *d*-tubocurarine, the purified and standardized product of curare obtained from the plant *Chondodendrom tomentosum*.[1] *d*-Tubocurarine has been completely replaced by more modern synthetic analogues.

d-Tubocurarine

The dose of *d*-tubocurarine required to produce 95% twitch block of at the adductor pollicis muscle, or ED_{95}, is 0.5 mg/kg. At that dose, the duration of action is typical of a long-duration agent (Table 20-2).[47]

Pharmacology

The molecule undergoes minimal metabolism so that 24 hours after its administration about 10% of the compound is found in the urine and 45% in the bile. Like most other **neuromuscular blocking** drugs, it is not extensively (30 to 50%) protein bound. Excretion is impaired in renal failure.

Cardiovascular Effects

Hypotension frequently accompanies the administration of *d*-tubocurarine even at doses $<ED_{95}$. The mechanism involved is mainly histamine release, and skin flushing is frequently observed. Autonomic ganglionic blockade may also play a minor role.

Age

Pharmacokinetic studies have been performed in all age groups, and the results are helpful in understanding the behavior of all nondepolarizing **agents** in patients at the extremes of age. The potency of *d*-tubocurarine on a milligram per kilogram basis does not vary greatly with age. Infants demonstrate

greater blockade than older children or adults if the same concentration of *d*-tubocurarine is applied. However, infants have an increased volume of distribution, when expressed in milliliters per kilogram of body weight, so that the same milligram per kilogram dose produces a reduced concentration. The net effet is similar blockade after a given milligram per kilogram dose in infants, older children, and adults (Table 20-3).[48] This phenomenon has also been observed with other **neuromuscular blocking agents**. However, the decreased glomerular filtration rate in the very young and the very old results in an increased elimination half-life and prolonged duration of action.[48] The onset of action is more rapid in the young as a result of a more rapid circulation time.

Burns

Patients with massive burns demonstrate resistance to *d*-tubocurarine and other nondepolarizing drugs that depends on the size of the burn and the time since injury.[49] Higher concentrations of the free drug are required to produce a given degree of twitch depression compared with nonthermally injured patients. Compared with normal subjects, the number of acetylcholine receptors is increased in muscles close to the site of burn injury, but also, to a lesser extent, in more distant muscles.[50]

Clinical Use

The long duration and cardiovascular effects of *d*-tubocurarine have restricted its use and constituted a stimulus for the production of alternative **agents**. Initially, this led to the introduction of pancuronium, which replaced the hypotension of *d*-tubocurarine with hypertension and tachycardia. More recently, drugs of intermediate duration (atracurium, cisatracurium, vecuronium, and rocuronium) with virtually no cardiovascular effects have almost eliminated the use of *d*-tubocurarine. When available, *d*-tubocurarine has been mainly confined to be used as a "precurarization" (3 mg/70 kg) before succinylcholine to reduce fasciculations and muscle pains. Rocuronium has largely replaced *d*-tubocurarine for this indication.

Alcuronium

Although it has never been available in North America, alcuronium still enjoys limited use in some countries. The ED_{95} is approximately 0.2 to 0.25 mg/kg. Intubating doses are usually limited to 0.3 mg/kg because of the long duration of action. Although it was introduced as an intermediate-duration drug, its recovery index (37 minutes) makes it a long-acting **neuromuscular blocking** agent.[51]

Atracurium

Atracurium is a bisquaternary ammonium benzylisoquinoline compound of intermediate duration of action. It is degraded via two metabolic pathways. One of these pathways is the Hofmann reaction, a nonenzymatic degradation with a rate that increases as temperature and/or pH increases. The second pathway is nonspecific ester hydrolysis. The enzymes involved in this metabolic pathway are a group of tissue esterases, which are distinct from plasma or acetyl cholinesterases.[52] The same group of enzymes is involved in the degradation of esmolol and remifentanil. It has been estimated that two thirds of atracurium is degraded by ester hydrolysis and one third by Hofmann reaction. Subjects with abnormal plasma cholinesterase have a normal response to atracurium.

The end products of the degradation of atracurium are laudanosine and acrylate fragments. Laudanosine has been reported as causing seizures in animals, but at doses largely exceeding the clinical range. No deleterious effect of laudanosine has been demonstrated conclusively in humans.[52] Laudanosine is excreted by the kidney. Acrylates have been shown to inhibit human cell proliferation in vitro.[53] However, the concentrations and exposure times required to obtain this effect are much greater than what is obtained normally in clinical practice.

Pharmacology

Atracurium is an intermediate-duration drug, with a terminal half-life of approximately 20 minutes. Termination of effect occurs during the elimination phase of the drug. Duration of action does not depend on age, renal function, or hepatic function.

The ED_{95} of atracurium is 0.2 to 0.25 mg/kg. The onset of action (3 to 5 minutes at 2 × ED_{95}) of equipotent doses is similar for atracurium, pancuronium, *d*-tubocurarine, and vecuronium. It is slower than succinylcholine. As with any **neuromuscular blocking** agent, onset of atracurium can be shortened if the dose is increased, but it is not recommended to exceed 0.5 mg/kg because of hypotension and histamine release. The duration of action is also dose-related. The time to 25% first twitch recovery after 0.5 mg/kg is approximately 30 to 40 minutes.

Cardiovascular Effects

Like *d*-tubocurarine, atracurium releases histamine in a dose-related manner. If large doses (≥0.5 mg/kg) are administered, hypotension, tachycardia, and skin flushing are frequent manifestations. Bronchospasm may also occur. These responses can be avoided by slow injection of atracurium over 1 to 3 minutes or by pretreatment with H_1 and H_2 receptor blockade. This histamine release, which occurs in virtually every subject given a large enough dose, should not be confused with an anaphylactic reaction, which is observed irrespective of dose in a small number of individuals. Anaphylactic reactions to atracurium have been described, but they do not appear to be more frequent than after other **neuromuscular blocking** drugs.[27]

Special Situations

Dosage requirements are similar in the elderly, younger adults, and children, presumably reflecting the organ independence of atracurium's elimination. Similarly, no dosage adjustment is required in individuals with renal or hepatic failure. As with other nondepolarizing **agents**, the dose must be increased in burn patients, partly because of increased protein binding and partly because of up-regulation of receptors, causing resistance at the endplate. In the obese patient, the dose of atracurium, as for all **neuromuscular blocking agents**, should be calculated based on lean body mass.

Clinical Uses

To obtain adequate intubating conditions, relatively large doses must be used (0.5 mg/kg), and laryngoscopy should be attempted only after 2 to 3 minutes. Cardiovascular manifestations of histamine release are often seen at that dose, and perfect intubating conditions are seen in only half the patients (Fig. 20-3).[8] Increasing the dose may improve intubating conditions, but at the expense of greater cardiovascular effects. For intubation, there has been a tendency to replace atracurium by **agents** with a shorter onset time and more cardiovascular stability, such as rocuronium. However, atracurium is convenient and versatile for maintenance of relaxation, either as a continuous infusion (5 to 10 μg/kg/min) or as intermittent injections (0.05 to 0.1 mg/kg every 10 to 15 minutes).

Cisatracurium

In an attempt to increase the margin of safety between the **neuromuscular blocking** dose and the histamine-releasing dose, a potent isomer of atracurium, cisatracurium, was identified. Like atracurium, its cardiovascular effects are manifest only at doses exceeding 0.4 mg/kg, but its ED_{95} (0.05 mg/kg) is much lower. As a result, manifestations of histamine release are not seen in practice. The metabolism of cisatracurium is similar to that of atracurium, with Hofmann and ester hydrolysis both playing a role.[52]

Pharmacology

Because cisatracurium is a potent drug, its onset time is longer than that of atracurium and longer still than that of rocuronium. For example, equipotent doses of cisatracurium (0.092 mg/kg) and rocuronium (0.72 mg/kg) had onset times of 4 minutes and 1.7 minutes, respectively.[54] The elimination half-life (22 to 25 minutes) is similar to that of atracurium,[55] so the duration of action for 2 × ED_{95} doses (0.1 mg/kg) is 30 to 45 minutes. However, in an attempt to accelerate onset, the recommended intubating dose is increased to 0.15 mg/kg. This dose is well below the threshold for histamine release, but the duration of action is prolonged to 45 to 60 minutes.

Because the doses required to obtain paralysis are considerably less for cisatracurium than for atracurium, less laudanosine and less acrylate byproducts are produced.[52,53] Thus, the concerns raised by the potential toxic effects of these metabolites are virtually eliminated.

Special Situations

Like atracurium, there is no need to adjust dosage in the elderly, children, or infants, when compared with young adults. The experience in burn patients is limited, but the same principles that are valid for atracurium are expected to apply. In obese individuals, the dose of cisatracurium should be calculated on the basis of ideal body weight.[56]

Side Effects

In contrast to atracurium, cisatracurium is devoid of histamine-releasing properties even at high doses (8 × ED_{95}). It is also devoid of cardiovascular effects. However, anaphylactic reactions have been described.[27]

Clinical Use

Cisatracurium may be used to facilitate tracheal intubation at doses equivalent to 3 to 4 times the ED_{95} (0.15 to 0.2 mg/kg) when manual ventilation is possible after induction of anesthesia and when the

duration of the procedure is expected to exceed 1 hour. Duration is shorter with lower doses, but onset time is prolonged and intubating conditions are less ideal. Neuromuscular blockade is easily maintained at a stable level by continuous intravenous infusion of cisatracurium (1 to 2 μg/kg/min) at a constant rate and does not change with time, suggesting the lack of a significant cumulative drug effect and lack of dependence on renal and/or hepatic clearance mechanisms.[57] The rate of recovery is independent of the dose of cisatracurium and the duration of the administration.

Because cisatracurium does not depend on end-organ function for its elimination, the drug appears suitable for administration in the intensive care unit (ICU). The infusion rates to keep patients paralyzed are greater than in the operating room (typically 5 μg/kg/min), with wide interindividual variability.[58] It is likely that prolonged exposure of the receptors to a neuromuscular blocking agent causes some up-regulation, with a corresponding requirement for a higher dose.[49]

Doxacurium

Doxacurium is a potent, long-acting benzylisoquinoline compound that is not degraded by Hofmann elimination or ester hydrolysis. It has a prolonged elimination half-life (1 to 2 hours) and depends on the kidney and the liver for its disposition. Thus, duration of action is prolonged in the elderly and in subjects with impaired renal or hepatic function. The ED_{95} for doxacurium is 25 μg/kg (Table 20-2).[59] Doxacurium has a limited place in clinical practice because of its very slow onset and long duration of action. Nevertheless, its cardiovascular stability may be useful in patients with ischemic heart disease who are undergoing prolonged anesthesia or long-term mechanical ventilation of the lungs. It is unsuitable for facilitating tracheal intubation or for providing skeletal muscle relaxation during brief surgical procedures. When infused for several days to patients in the ICU, recovery after stopping the infusion exceeded 10 hours.

Gallamine

Gallamine was introduced in 1948 and has only historical interest. It is a low potency nondepolarizing drug (ED_{95} = 2 mg/kg) with a long duration of action. Gallamine produces significant tachycardia because of a vagolytic effect, even at doses associated with incomplete blockade at the adductor pollicis muscle. It is effective when used to prevent succinylcholine-induced fasciculations.[20]

Gantacurium

Gantacurium is a new compound, still under investigation. It is a nondepolarizing drug and belongs to the class of asymmetric mixed-onium chlorofumarates. Its main degradation pathway involves cysteine in the plasma and is independent of plasma cholinesterase. The ED_{95} in humans is approximately 0.19 mg/kg.[60] Cardiovascular effects are observed at doses exceeding 3 × ED_{95}, and are most probably related to histamine release. At doses anticipated to be required for tracheal intubation (0.4 to 0.6 mg/kg), onset at the adductor pollicis muscle is 1.5 minutes and duration to 25% T_1 recovery is 8 to 10 minutes, comparable with that of succinylcholine.

Metocurine

Metocurine, produced by methylation of two hydroxy groups of *d*-tubocurarine, is twice as potent as the parent compound

and produces less histamine release. Its ED_{95} is approximately 0.3 mg/kg.[47] Its duration of action is comparable with that of *d*-tubocurarine, making it a long-acting agent. Metocurine enjoyed a brief period of popularity before the introduction of atracurium and vecuronium. Metocurine and pancuronium combined were found to be synergistic with opposing cardiovascular effects, and the mixture was recommended for use in patients with severe cardiovascular disease. However, the introduction of shorter-duration alternatives without cardiovascular effects has made metocurine obsolete.

Mivacurium

Mivacurium is a benzylisoquinoline derivative with a short duration of action that is hydrolyzed by plasma cholinesterase, like succinylcholine.[61] Contrary to succinylcholine, however, mivacurium produces nondepolarizing blockade. The drug is presented as a mixture of three isomers. Two, the cis-trans and trans-trans, have short half-lives, but the cis-cis isomer has a much longer half-life (Table 20-3). The pharmacology of mivacurium is governed largely by the behavior of the trans-trans and cis-trans isomers, because the cis-cis isomer accounts for only 6% of the mixture and has less potent that the other two isomers.

Pharmacology

The ED_{95} of mivacurium has been estimated in the range 0.08 to 0.15 mg/kg (Table 20-2). Intubating doses are 0.2 or 0.25 mg/kg but intubating conditions are not as good as with succinylcholine.[62] Onset time is surprisingly long for a drug whose active isomers have a terminal half-life of <2 minutes. At 2 to 3 × ED_{95}, twitch disappears in 2.5 to 4 minutes.[61] This long onset time is probably the result of the high potency of mivacurium.[46] Recovery to 25% does not depend heavily on dose, being in the range of 15 to 25 minutes for doses of 0.15 to 0.25 mg/kg. The infusion rate to maintain blockade constant does not vary with time, and recovery is as rapid after many hours of infusion than after a bolus dose.[61]

Side Effects

Like atracurium, mivacurium releases histamine in a dose-related fashion. Hypotension, tachycardia, and cutaneous signs, such as erythema and flushing, are seen frequently when doses are increased to 0.2 mg/kg or more. These histamine-related effects are short-lived (2 to 3 minutes) and should not normally be considered a manifestation of anaphylaxis, which is a rare event. Bronchospasm is rare. Manifestations of histamine release may be decreased if the drug is either given slowly (in >30 seconds) or in divided doses (0.15 mg/kg followed 30 seconds later by 0.1 mg/kg).

Special Situations

In infants and children the ED_{95} is approximately the same as in adults, but onset of block and recovery are more rapid.[63] Cardiovascular effects are not as important as in adults, so doses up to 0.3 mg/kg have

been used. The infusion rate required to maintain blockade is greater in children than in adults, and less in the elderly than in younger adults.

Burns

In burn patients, up-regulation of the receptors, and to a lesser extent increased protein binding, causes a resistance to all nondepolarizing **neuromuscular blocking agents**. However, for mivacurium, the situation is different because plasma cholinesterase activity is decreased in burn patients. The net effect is either a normal or even an enhanced effect of usual doses.[64]

Reversal

Administration of anticholinesterase **agents** after mivacurium has been controversial. Neostigmine has two opposing effects on mivacurium: it inhibits plasma cholinesterase, thus interfering with the breakdown of mivacurium, but it also reverses nondepolarizing blockade. In fact, neostigmine has been shown to delay recovery if given during intense mivacurium **neuromuscular** block,[65] but to accelerate recovery if signs of spontaneous recovery are present (two twitches or more present). Edrophonium does not interfere with plasma cholinesterase activity and was found to accelerate recovery, even when given when blockade is profound (one twitch in the train-of-four).[65] Mivacurium reversal has been suggested to be unnecessary because spontaneous recovery is rapid. However, residual block may be seen, particularly if large doses of mivacurium are used up to the end of anesthesia.

Plasma Cholinesterase

Mivacurium is metabolized by plasma cholinesterase somewhat more slowly than succinylcholine. The conditions associated with a decrease plasma cholinesterase activity known to affect succinylcholine metabolism also alter mivacurium duration of action.

Clinical Use

Mivacurium is no longer available in North America, but it is used in other parts of the world. It is well suited to surgical procedures requiring brief muscle relaxation, particularly those in which rapid recovery is required, such as ambulatory and laparoscopic surgery. However, it is not recommended for rapid-sequence induction. Cardiovascular effects may be avoided by administering the drug slowly or by splitting the dose into two injections 30 seconds apart. Small doses of mivacurium (0.04 to 0.08 mg/kg) have been suggested to facilitate insertion of a laryngeal mask airway. Conditions and success rate are usually better than in the absence of **neuromuscular blocking** agent. Maintenance of relaxation is accomplished more easily by constant infusion (5 to 7 µg/kg/min in young and middle-aged adults) than by intermittent bolus injection. This infusion rate has to be increased in children and reduced in the elderly. In children, mivacurium has a faster onset of action and more rapid recovery than in adults, so the drug can be used for intubation and maintenance of relaxation for short procedures.[63]

Pancuronium

Pancuronium belongs to a series of bisquaternary aminosteroid compounds. It is metabolized to a 3-OH compound, which has one-half the **neuromuscular blocking** activity of the parent compound. The ED_{95} of

pancuronium is 0.07 mg/kg. The duration of action is long, being 1.5 to 2 hours after a 0.15 mg/kg dose. Clearance is decreased in renal and hepatic failure, demonstrating that excretion depends on both organs. The onset of action is more rapid in infants and children than in adults, and recovery is slower in the elderly.

Cardiovascular Effects

Pancuronium is associated with increases in heart rate, blood pressure, and cardiac output, particularly after large doses ($2 \times ED_{95}$). The cause is uncertain but includes a vagolytic effect at the postganglionic nerve terminal, a sympathomimetic effect as a result of **blocking** of muscarinic receptors that normally exert some braking on ganglionic transmission, and an increase in catecholamine release. Pancuronium does not release histamine.

Clinical Use

The slow onset of action of pancuronium limits its usefulness in facilitating tracheal intubation. Administration in divided doses, with a small dose given 3 minutes before induction of anesthesia (priming principle), produces a small but measurable acceleration. However, the intermediate-acting compounds are more suitable when succinylcholine is contraindicated. In cardiac anesthesia, pancuronium has enjoyed popularity because it counteracts the bradycardic effect of high doses of opioids. With the increased tendency toward

early extubation in cardiac surgery, the appropriateness of pancuronium in this setting must be re-evaluated. The use of pancuronium instead of rocuronium is associated with a greater incidence of muscular weakness after cardiac surgery,[66] and reversal in this setting should be considered seriously. The continued popularity of pancuronium relates to cost: generic pancuronium is cheaper than other nondepolarizing relaxants. In noncardiac patients, its use is associated with a high incidence of residual block in the postanesthesia care unit, even when reversal is given (Table 20-1).[9,67] Pancuronium **neuromuscular** block is more difficult to reverse than that of the intermediate duration **agents**.[68]

Pipecuronium

Pipecuronium was developed in an effort to obtain a pancuronium without cardiovascular side effects. Its ED_{95} is slightly less (0.05 mg/kg) than that of pancuronium, and it is virtually without any cardiovascular effects. However, pipecuronium soon became obsolete because it had the drawbacks of long-acting **agents** (difficulty to reverse, residual paralysis, lack of versatility), and the absence of cardiovascular effects was also seen with the shorter-acting vecuronium and rocuronium.

Rapacuronium

Rapacuronium is also an aminosteroid compound that was introduced for clinical use in 1999. It was withdrawn in 2001 because of rare, but severe, cases of bronchospasm after intubation. Being less potent than rocuronium, it had a more rapid onset of action. Following 1.5 mg/kg, good-to-excellent intubation

conditions were produced at 60 seconds, mean clinical duration was 17 minutes, and spontaneous recovery to train-of-four ratio of 0.7 occurred in 35 minutes.[69] The intubating conditions were not as good as with succinylcholine and the duration of action was longer. Rapacuronium is metabolized to an active 17-OH derivative (ORG 9488) that has twice the **neuromuscular blocking** activity of the parent compound and is excreted slowly via the kidneys.

Rapacuronium produced mild dose-related tachycardia and hypotension. Increases in airway pressure and bronchospasm were observed in more patients given rapacuronium than succinylcholine.[69] The mechanism for this effect is not an allergic or histamine-related reaction, but is most likely related to the effect of rapacuronium on M2 and M3 muscarinic receptors in the lung. Activation of the postsynaptic M3 receptors by acetylcholine produces bronchosconstriction in the lungs, and the effect is terminated by presynaptic M2 receptors that counteract this effect. Rapacuronium has the potential to block both receptors, but it has a greater affinity for the M2 receptor. The concentrations required for M2 blockade are well within the clinical range, while much more is required for M3 inhibition. The net effect is that if M2 receptors are blocked selectively, for example, in susceptible individuals, bronchoconstriction by activation of the M3 receptors is unopposed.[70] Other **neuromuscular blocking agents**, such as vecuronium and cisatracurium, have similar differential effects on the M2 and M3 receptors, but at concentrations higher than encountered clinically.[70]

Rocuronium

Rocuronium is an aminosteroid compound with structural similarity with vecuronium and pancuronium. Its duration of action is comparable with that of vecuronium, but its onset is shorter.

Pharmacology

Plasma concentrations of rocuronium decrease rapidly after bolus injection because of hepatic uptake.[71] Thus, the duration of action of the drug is determined chiefly by redistribution, rather than by its rather long terminal elimination half-life (1 to 2 hours; Fig. 20-10). Metabolism to 17-deacetylrocuronium is a very minor elimination pathway. Most of the drug is excreted unchanged in the urine, bile, or feces.[71]

With an ED_{95} of 0.3 mg/kg, rocuronium has one-sixth the potency of vecuronium, a more rapid onset, but a similar duration of action and similar pharmacokinetic behavior. With equipotent doses, rocuronium onset at the adductor pollicis muscle is much faster than that of cisatracurium, atracurium, and vecuronium (Fig. 20-11).[46] After doses of 0.6 mg/kg ($2 \times ED_{95}$) maximal block occurs in 1.5 to 2 minutes. In a multicenter study of 349 patients, intubating conditions at 60 seconds after 0.6 mg/kg rocuronium were good to excellent in 77% of cases. To obtain results similar to those after 1 mg/kg succinylcholine, the dose of rocuronium had to be increased to 1.0 mg/kg, which provided 92% good or excellent conditions.[72] However, the duration of action is longer than for succinylcholine, ranging between 30 and 40 minutes for a 0.6-mg/kg dose to approximately 60 minutes after 1 mg/kg in adults. Thus, rocuronium is an intermediate-duration drug.

As for other nondepolarizing agents, the onset of action of rocuronium is more rapid at the diaphragm and adductor laryngeal muscles than at the adductor pollicis muscle,[73] probably a result of a greater blood flow to centrally located muscles. Laryngeal adductor muscles are important in anesthesia because they close the vocal cords and insufficient relaxation prevents easy passage of the tracheal tube. Laryngeal adductor muscles are resistant to the effect of rocuronium, and the plasma concentration required for equivalent blockade is greater at the larynx than at the adductor pollicis muscle.[74] The same is true of the diaphragm, which is resistant to the effect of rocuronium and other neuromuscular blocking agents. Recovery is faster at the diaphragm and larynx than at the adductor pollicis muscle.[75]

Cardiovascular Effects

No hemodynamic changes (blood pressure, heart rate, or ECG) were seen in humans, and there were no increases in plasma histamine concentrations after doses of up to 4 × ED_{95} (1.2 mg/kg).[76] Only slight hemodynamic changes are observed during coronary artery bypass surgery. Anaphylactic reactions have been described, and a French study indicated that these events occurred more frequently with rocuronium than with other neuromuscular blocking agents,[27] contrary to the findings of an Australian study.[77] However, it now appears that many of these reports might not be a true anaphylactic reaction to rocuronium because up to 50% of the general population show a positive intradermal or pick test to the drug.[78] Clearly, many patients who were investigated for a possible anaphylactic reaction were falsely labeled allergic to the drug because of the high rate of false-positive tests. It is possible that overdiagnosis has played a role in the relatively high incidence of rocuronium anaphylaxis reported in Norway (29 cases in 150,000 administrations, or 1:5,000)[79] or in France,[27] while reports from other Nordic countries suggest a much lower incidence (7 cases in 800,000 administrations, or <1:100,000).[79]
Another hypothesis that was put forward recently is sensitization of patients by over-the-counter cough medication containing pholcodine. In a study comparing subjects from Norway, where the number of reported anaphylactic cases is high, and Sweden, where those reports are virtually nonexistent, it was found that a large proportion of Norwegians was sensitized to pholcodine, but this sensitization did not occur in Swedes.[80] Pholcodine is available as an antitussive in cough syrups in certain countries like Norway, France, Ireland, the United Kingdom, and Australia. It is not available in Sweden, Denmark, Germany, the United States, and Canada. In the United States, the incidence of anaphylactic reactions to

rocuronium and vecuronium may be as low as 1:1,000,000.[81] It is hypothesized that cross-sensitization may occur between pholcodine and neuromuscular blocking agents such as rocuronium and succinylcholine. However, its should be remembered that the role of pholcodine in the context remains a hypothesis, and the incidence of anaphylactic reactions to rocuronium remains very low, even in countries where pholcodine is available. Thus, current evidence suggests that withholding rocuronium because of the fear of anaphylactic reactions is unjustified.

Special Situations

The potency of rocuronium has been reported to be slightly greater in women than in men, the ED_{95} being 0.27 and 0.39 mg/kg, respectively, with an increased duration in women.[82] Some ethnic groups are more sensitive to the drug. Chinese subjects living in Vancouver were found to be more sensitive than whites.[83] As with other nondepolarizing drugs, potency has been reported to vary according to geographical distribution. Most studies reported a greater potency in North America compared with Europe,[84] with one report showing a potency of rocuronium in mainland China as intermediate between European and American values.[84] Children (2 to 12 years old) require more rocuronium and duration of action is less. Onset of action is shorter in the pediatric than in the adult population. For example, a dose of 1.2 mg/kg provides an onset time (39 seconds) comparable with that of succinylcholine, 2 mg/kg, and mean duration of action is 41 minutes.[85] Thus, the recommended doses are 0.9 to 1.2 mg/kg in this age group. Rocuronium is more potent in infants than in older children. Doses of 0.6 mg/kg have a longer duration in neonates (<1 month) than in infants (5 to 12 months), so a reduced dosage (0.45 mg/kg) is recommended.[86] Rocuronium may be used for rapid-sequence induction as succinylcholine is relatively contraindicated because of the possible presence of undiagnosed muscle dystrophy in pediatric patients, especially in boys.[34] The use of rocuronium in large doses (1.2 mg/kg) might become widespread in all age groups for rapid-sequence induction if and when the selective binding agent sugammadex becomes available (see "Sugammadex").

In elderly patients, the ED_{95} is similar to that found in younger adults, but the duration of action is prolonged slightly.[87] Rocuronium has an increased terminal half-life in renal-failure patients, probably because of its partial renal elimination, but this translates into very minor, if any, prolongation of block.[88] In hepatic disease, the slower uptake and elimination of rocuronium by the liver tends to prolong the duration of action of the drug, but this is compensated to some extent by the larger volume of distribution.[89]

Clinical Use

The rapid onset and intermediate duration of action makes this agent a potential replacement for succinylcholine in conditions where rapid tracheal intubation is indicated. However, large doses (>1 mg/kg) are required, with the drawback being a prolonged duration of action. Contrary to succinylcholine, the option to wait for spontaneous breathing to resume before hypoxia is manifest does not exist with rocuronium. To shorten the onset time, the "priming principle," which involves the administration of a small dose of rocuronium usually 3 minutes before induction, has been advocated. Unfortunately, the optimal priming dose, that is the largest dose that will not produce symptoms of weakness in the awake patient, is rather small. As with defasciculating doses before succinylcholine, it is not recommended to administer more than $0.1 \times ED_{95}$,[28] which, in the case of rocuronium, amounts to 0.03 mg/kg. Such a small dose has minimal effects on onset times provided by much larger doses (0.6 to 1.0 mg/kg). However, priming might have an effect if the intubating dose is small (0.45 mg/kg). A "timing

principle" has been described in which 0.6 mg/kg rocuronium is given *before* the induction agent, which is administered at the onset of ptosis. Considering that loss of consciousness does not occur immediately after injection of the induction agent, this technique is not recommended. Rocuronium and thiopental do not mix. They form a precipitate when they are in the same intravenous line. If thiopental is used for induction of anesthesia, the line must be flushed carefully before rocuronium is given.

Rocuronium has gradually replaced vecuronium as an intermediate-duration relaxant because of its more rapid onset. Initial doses of 0.6 mg/kg intravenously will usually produce good intubating conditions within 90 seconds. Duration of action is 30 to 40 minutes. Smaller doses (typically, 0.45 mg/kg) have a shorter duration of action, but time to intubation must be increased. Subsequent doses of 0.1 to 0.2 mg/kg will provide clinical relaxation for 10 to 20 minutes. Alternatively, rocuronium might be given by continued infusion, titrated with the help of a nerve stimulator. Infusion rates are in the range 5 to 10 μg/kg/min.[57] Recovery after infusions is slower than after bolus doses.

Vecuronium

Vecuronium is an intermediate-duration aminosteroid **neuromuscular** relaxant without cardiovascular effects. Its ED_{95} is 0.04 to 0.05 mg/kg. Its duration and recovery characteristics are comparable with those of rocuronium. However, its onset of action is slower.

Pharmacology

Vecuronium is a monoquaternary ammonium compound produced by demethylation of the pancuronium molecule. Vecuronium undergoes spontaneous deacetylation to produce 3-OH, 17-OH, and 3,17-$(OH)_2$ metabolites. The most potent of these metabolites, 3-OH vecuronium, about 60% of the activity of vecuronium, is excreted by the kidney and may be responsible, in part, for prolonged paralysis in patients in the ICU. Like rocuronium, vecuronium has been found less potent and with a shorter duration of action in men than in women, probably because of a greater volume of distribution in men.

Duration of action of vecuronium, like that of rocuronium, is governed by redistribution, not by elimination (Fig. 20-10). Attempts have been made to speed the onset of action by using the priming principle, that is, by administering a small, subparalyzing dose several minutes before the principal dose is given. With the availability of rocuronium, which has a more rapid onset of action than that of vecuronium, "priming" becomes an obsolete practice.

Cardiovascular Effects

Vecuronium usually produces no cardiovascular effects with clinical doses. It does not induce histamine release. Bradycardia has been described with high-dose opioid anesthesia, and this might be the reflection of the opioid effect. Allergic reactions have been described, but no more frequently than after the use of other **neuromuscular blocking** drugs.[27,81]

Clinical Use

The cardiovascular neutrality and intermediate duration of action make vecuronium a suitable agent for use in patients with ischemic heart disease or those undergoing short, ambulatory surgery. As with

rocuronium, care should be taken when vecuronium is administered immediately after thiopental because a precipitate of barbituric acid may be formed that may obstruct the intravenous cannula.

Large doses (0.1 to 0.2 mg/kg) can be used to facilitate tracheal intubation instead of succinylcholine. For maintenance of relaxation, vecuronium may be given using intermittent boluses, 0.01 to 0.02 mg/kg, or by continuous infusion at a rate of 1 to 2 μg/kg/min. However, the rate of spontaneous recovery of neuromuscular function is slowerafter administration

by infusion than by intermittent boluses.[90] Vecuronium has now largely been replaced by the more rapid rocuronium.

Drug Interactions

Interactions between neuromuscular blocking drugs and several anesthetic and nonanesthetic drugs have been suggested. Although some interactions have been confirmed, many remain as isolated case reports or theoretical possibilities. Only some of the most clinically relevant interactions will be discussed here.

Anesthetic Agents

Inhalational Agents

The anesthetic vapors potentiate neuromuscular blockade in a dose-related fashion. Studies attempting to quantify the magnitude of this effect have led to conflicting results because the time factor is also important. The older halogenated agents halothane, enflurane, and isoflurane may take 2 hours or more to equilibrate with muscle, so in practice the potentiating effect of these vapors might not be immediately apparent. At similar minimum alveolar concentration (MAC), enflurane appears to potentiate nondepolarizing blockade more than does isoflurane, which in turn potentiates to a greater extent than halothane. The newer agents sevoflurane and desflurane equilibrate more rapidly with muscle, but the effect may be measurable only after 30 minutes or more. For example, the duration of action of a bolus dose of mivacurium given at induction of anesthesia is not altered by the presence of sevoflurane (1 MAC). However, the infusion rate required to maintain block decreases by 75% over the next 1.5 hours, compared with no change under propofol anesthesia.[91] The degree of potentiation increases with the concentration of sevoflurane. Recovery rate is longer in the presence of sevoflurane, even if the infusion rate of mivacurium was less. There is evidence that desflurane might have a greater potentiating effect on the neuromuscular junction than sevoflurane.[92]

Nitrous oxide (70% inspired) has been considered as having no effect on neuromuscular blockade. Recent evidence suggests that the presence of nitrous oxide has a slight potentiating effect on neuromuscular block, decreasing the ED_{50} of rocuronium by approximately 20%.[93]

The mechanism of action of potentiation by halogenated agents is uncertain, but it appears that they produce their effects at the neuromuscular junction. Isoflurane and sevoflurane inhibit current through the nicotinic receptor at the neuromuscular junction, and this inhibition is dose-dependent.[94]

Intravenous Anesthetics

Although some slight potentiation of neuromuscular blockade has been demonstrated with high doses of most intravenous induction agents in animals, clinical doses of drugs such as midazolam, thiopental, propofol, fentanyl, and ketamine have little or no neuromuscular effect in humans.

Local Anesthetics

Lidocaine, procaine, and other local anesthetic agents produce neuromuscular blockade in their own right as well as potentiating the effects of depolarizing and nondepolarizing neuromuscular blocking drugs. Contrary to the findings of other studies, a longer duration of action of vecuronium was found in patients under general anesthesia with an epidural catheter injected with mepivacaine.[95] The exact mechanisms for this interaction are uncertain, but it is unlikely that the systemic levels of local anesthetic are sufficient to produce this effect at the neuromuscular junction.

Interactions Between Nondepolarizing Blocking Drugs

Combinations of two nondepolarizing neuromuscular blocking drugs are either additive or synergistic, depending on which two drugs are involved. Addition occurs when the total effect equals that of equipotent doses of each drug. For instance, pancuronium and vecuronium have an additive interaction.[96] An ED_{95} of either pancuronium (0.07 mg/kg) or vecuronium (0.05 mg/kg) yields 95% blockade. Half the ED_{95} of pancuronium (0.035 mg/kg) administered with half the ED_{95} of vecuronium (0.025 mg/kg) will also produce 95% block. However, some combinations are synergistic; that is, their combined effect is greater than if an equipotent dose of either one of the constituents is given alone. For example, cisatracurium (ED_{95} = 0.05 mg/kg) and rocuronium (ED_{95} = 0.3 mg/kg) will produce a greater blockade than equipotent amounts of each drug given alone. If half the ED_{95} of cisatracurium (0.025 mg/kg) is administered with half the ED_{95} of rocuronium (0.15 mg/kg), the effect will be >95% twitch depression. To get 95% block, only approximately one-fourth the ED_{95} of each drug needs to be given together; that is, cisatracurium, 0.0125 mg/kg with rocuronium, 0.075 mg/kg.[97] Generally, combinations of chemically similar drugs—for example, pancuronium- vecuronium, *d*-tubocurarine-metocurine, and atracurium- mivacurium—have additive effects. Combinations of dissimilar agents tend to show potentiation, but the rule is not always followed. The first such synergism was demonstrated for pancuronium-metocurine combinations, and the mixture was advocated for its lack of cardiovascular effects. The use of combinations may be recommended to reduce cost or to take advantage of the properties of two drugs. For example, synergism occurs between mivacurium and rocuronium, and the mixture retains the fast onset of rocuronium, while having the short duration of action of mivacurium.

The mechanism by which two drugs produce a greater effect than either one alone is uncertain. Synergism is expected between mivacurium and pancuronium because of the inhibition of plasma cholinesterase that pancuronium produces, thus accentuating the effect of mivacurium. However, such a simple mechanism is absent in most cases. Surprisingly, when drug mixtures are applied to receptors in vitro, no potentiation is observed.[98]

Interactions of a different nature occur when administration of a nondepolarizing agent is followed by injection of another nondepolarizing agent. Usually, the duration of action of the second agent is that of the first drug given. For example, if vecuronium, an intermediate-acting agent, is given after the long-acting pancuronium, it has a long duration of action.[99] On the contrary, if vecuronium is the first drug, pancuronium given as a top-up dose has an intermediate duration of action. Thus, switching from a long-duration agent to an intermediate-duration drug to obtain paralysis of intermediate duration at the end of a case will not provide paralysis of intermediate duration. The reason why the characteristics of the first agent given are determinant is that the size of the loading dose is greater than that of the maintenance dose, so that even when the second dose is given, the majority of receptors is still occupied by the first drug.

Nondepolarizing-Depolarizing Interactions

Depolarizing and nondepolarizing relaxants are mutually antagonistic. When *d*-tubocurarine or other nondepolarizing **agents** are given before succinylcholine to prevent fasciculations and muscle pain, the succinylcholine is less potent and has a shorter duration of action.[22] The exception is with pancuronium because it inhibits plasma cholinesterase. However, nondepolarizing drugs are somewhat more effective when administered after the effect of succinylcholine has worn off, compared with no prior succinylcholine.[17] Finally, the response to a small dose of succinylcholine at the end of an anesthetic in which a nondepolarizing agent has been used is

difficult to predict. It may either antagonize or potentiate the blockade, depending on the degree of nondepolarizing block. Antagonism is more likely if blockade is deep and potentiation if blockade is shallow. If an anticholinesterase agent has been given, then the effect of the succinylcholine is potentiated because of inhibition of plasma cholinesterase.

Antibiotics

Neomycin and streptomycin are the most potent of the aminoglycosides in depressing **neuromuscular** function.[100] The polymyxins also depress **neuromuscular** transmission.[100] These antibiotics are no longer used frequently. Other aminoglycosides (e.g., gentamicin, netilmicin, tobramycin) also potentiate nondepolarizing **neuromuscular** blockade. They prolong the action of steroidal **neuromuscular agents**, but their effect on benzylisoquinoline compounds is less apparent.[101] The lincosamides clindamycin and lincomycin have prejunctional and postjunctional effects, but prolongation of blockade by clindamycin is unlikely to occur clinically unless large doses are used. The penicillins, cephalosporins, tetracyclines, and erythromycin are devoid of **neuromuscular** effects at clinically relevant doses. Metronidazole does not appear to have clinically significant effects at the **neuromuscular** junction.

Anticonvulsants

Acute administration of phenytoin produces augmentation of neuromuscular block.[102] Resistance to pancuronium, metocurine, vecuronium, and rocuronium has been demonstrated in patients receiving chronic anticonvulsant therapy with carbamazepine or phenytoin.[103,104] The requirements for atracurium, mivacurium, and cisatracurium are the same or increased slightly by chronic administration of anticonvulsant drugs.[105] A least part of the phenomenon has a pharmacokinetic origin. In patients with chronic carbamazepine therapy, the clearance of vecuronium was found to be increased and its terminal half-life decreased.[103]

Cardiovascular Drugs

Beta-blocking drugs and calcium channel antagonists have been found to have neuromuscular effects in vitro, but in practice, the duration of action of neuromuscular blocking agents is not altered in patients taking these drugs chronically.[104] Ephedrine given at induction of anesthesia has been found to accelerate onset of action of rocuronium while esmolol prolongs onset time.[106] The mechanism for this effect is probably by alteration of drug delivery to the site of action by changes in cardiac output. It is possible to take advantage of this phenomenon to improve intubating conditions. Use of ephedrine, 5 to 10 mg in the average adult, at induction has been shown to improve intubating conditions provided by rocuronium.[107]

Magnesium

Calcium is required for the release of acetylcholine,[12] and magnesium antagonizes this effect. In doses of 30 mg/kg at induction followed by 10 mg/kg/hr, magnesium was found to reduce maintenance rocuronium requirements by 50% and to increase recovery times.[108] Similar effects have been reported with other nondepolarizing agents. Previous administration of magnesium abolishes succinylcholine-induced fasciculations, but it does not prolong the duration of neuromuscular blockade.[109]

Miscellaneous

Metoclopramide inhibits plasma cholinesterase and thus prolongs the action of succinylcholine and mivacurium. Inconsistent interactions have been described for diuretics, digoxin, and corticosteroids, probably because these drugs induce chronic fluid and electrolyte shifts, the magnitude of which depends on the condition being treated.

Altered Responses to Neuromuscular Blocking Agents

Intensive Care Unit

Neuromuscular blocking agents are useful in the ICU to facilitate mechanical ventilation, and their use is frequent in patients requiring ventilation in the prone position, permissive hypercapnia, high positive end-expiratory pressure, and elevated airways pressure.[110] It is essential to provide sedation to patients who receive paralyzing agents, to prevent discomfort associated with the inability to move. Enthusiasm for the liberal use of neuromuscular blocking agents in the ICU has waned considerably over the past 10 to 20 years because of several reports of critically ill patients who demonstrated residual weakness for unexpectedly long periods after discontinuation of a neuromuscular blocking agent. In some, recovery took several months.[111] Pancuronium and vecuronium have been used most frequently, but recent

descriptions of similar syndromes after atracurium and cisatracurium suggest that the frequency of reports of weakness reflects the popularity of the drugs rather than a particular association with steroid-based compounds. Electromyographic studies have shown variable lesions from myopathy to axonal degeneration of motor and sensory fibers. The picture is complicated by the syndrome of "critical illness neuropathy," which occurs in patients with sepsis and multiorgan failure, even in individuals not given **neuromuscular blocking agents**. Administration of corticosteroids is also considered a risk factor.[110] Symptoms include failure to wean from mechanical ventilation, limb weakness, and impaired deep tendon reflexes, but sensory function is usually not affected. There are no controlled clinical studies to allow the several initiating factors to be identified and matched with particular syndromes. In the absence of more definitive studies, it is recommended to administer **neuromuscular blocking agents** only to patients who cannot be managed otherwise, to limit the duration of administration to a few days or less, to use only the dose that is necessary, and to interrupt temporarily the administration of the **neuromuscular blocking** agent every day or so.[110]

Studies in ICU patients in whom the administration of relaxant was adjusted according to strict **neuromuscular** monitoring criteria have shown considerable variation in the requirement for **neuromuscular blocking** agent to maintain the same effect among patients and a wide within-patient pharmacokinetic variability.[58] Vecuronium and rocuronium have been associated with prolonged recovery times. For example, a mean of 3 hours was found between the end of rocuronium infusion and a train-of-four ratio of 0.7.[112] With cisatracurium, this interval was shorter (approximately 1 hour) and less variable.[58] Drug requirement is variable from patient to patient, is usually greater than in the operating room, and tends to increase with time. These reports suggest the need for more careful monitoring of **neuromuscular** block in ICU patients, although the optimal method and level of block to be achieved are uncertain. It is suggested to titrate **neuromuscular blocking agents** to the minimum infusion rate that will optimize oxygenation.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease in which circulating antibodies produce a functional reduction in the number of postsynaptic acetylcholine receptors.[113]

Diagnosis and Management

The hallmark of myasthenia gravis is fatigue. Presentation is extremely varied but typically, ocular symptoms, such as diplopia and ptosis, occur first. Bulbar involvement is usually seen next. Patients may proceed to have extremity weakness and respiratory difficulties.[113] The characteristic EMG finding in myasthenia gravis is a voltage decrement to repeated stimulation at 2 to 5 Hz. This finding is also characteristic of nondepolarizing blockade in nonmyasthenic individuals. Edrophonium, 2 to 8 mg,

produces brief recovery from myasthenia gravis and can be used as a diagnostic test. Finally, up to 80% of patients have an increased titer of the acetylcholine receptor antibody.

Treatment is largely symptomatic. Anticholinesterase **agents** such as pyridostigmine are used to increase neurotransmission at the **neuromuscular** junction. Corticosteroids and immunotherapy with azathioprine might produce long-term improvement. Plasmapheresis might be effective by eliminating the circulating antibody. Finally, many myasthenic patients have an associated thymoma, and surgical removal of the thymus may be indicated.[113]

Response to Neuromuscular Blocking Agents

Patients with myasthenia gravis are usually resistant to succinylcholine, with larger than usual doses required to produce complete blockade. This effect might be offset by the inhibition of plasma cholinesterase activity provided by pyridostigmine. Sensitivity to nondepolarizing **neuromuscular blocking** drugs is increased to a variable extent, depending on the severity of the disease. The ED_{95} of vecuronium was found to be decreased by more than half in myasthenic patients, and the response of the orbicularis oculi muscle is depressed even more than that of the adductor pollicis muscle, reflecting some degree of ocular involvement.[114]

Management of Anesthesia

Traditionally, **neuromuscular blocking** drugs have been avoided in the patient with myasthenia gravis by the use of inhalational vapors with or without local anesthesia. More recently, there have been several reports of the successful use of small, titrated doses of atracurium, mivacurium, vecuronium, or rocuronium, administered under careful **neuromuscular** monitoring.[113] The effect of reversal drugs might be less than expected because myasthenic patients already receive drugs that produce cholinesterase inhibition. Thus, it is preferable to continue mechanical ventilation until spontaneous recovery is manifest.

After thymectomy, the need for mechanical support of ventilation can usually be predicted from preoperative lung function tests. The dose of anticholinesterases should be adjusted and is usually is reduced for 1 to 2 days after surgery.

Myotonia

Myotonia is characterized by an abnormal delay in muscle relaxation after contraction. Several forms have been described: myotonic dystrophy (dystrophia myotonica, myotonia atrophica, Steinert disease), myotonia congenita (Thomsen disease), hyperkalemic periodic paralysis, and paramyotonia congenita.

Diagnosis

Repeated nerve stimulation leads to a gradual but persistent increase in muscle tension. The EMG is pathognomonic; myotonic after-discharges are seen in peripheral muscle, consisting of rapid bursts of potential produced by tapping the muscle or moving the needle. They produce typical “dive-bomber” sounds on the loudspeaker.

Response to Neuromuscular Blocking Agents

The characteristic response to succinylcholine is a sustained, dose-related contracture that may make ventilation difficult for several minutes. Muscle membrane fragility may be responsible for the exaggerated hyperkalemia that is produced after succinylcholine.[34] Most case reports suggest that the response to nondepolarizing drugs is normal. However, myotonic responses have been observed after reversal with neostigmine.

Anesthesia

Succinylcholine is best avoided. Short- or intermediate-duration nondepolarizing **agents** may be used in usual doses with careful **neuromuscular** monitoring. Reversal **agents** are best avoided. Thus, mechanical ventilation should be maintained until the effects of nondepolarizing **agents** have worn off completely.

Muscular Dystrophy

The muscular dystrophies are a group of many diseases, with variability in presentation and typical age at onset of symptoms. The most common of these is the Duchenne-type muscular dystrophy (DMD), an X-linked hereditary disease that usually becomes apparent in childhood. Other types of muscular dystrophy include Becker, limb-girdle, fasciohumeral, Emery-Dreifuss, nemaline rod, and oculopharyngeal dystrophy. There have been several reports of cardiac arrest after administration of succinylcholine in children, often associated with hyperkalemia. Resuscitation was found to be difficult, and several of these cases were fatal.[34] The most likely explanation for these adverse events is previously undiagnosed, latent, muscular dystrophy.

Response to Neuromuscular Blocking Agents

In most case reports, the response to nondepolarizing **agents**, such as vecuronium, atracurium, and mivacurium, has been described as normal, although there have been sporadic instances of increased sensitivity. There are little data on the response to anticholinesterases. There is considerable controversy over whether DMD patients are susceptible to malignant hyperthermia.

Anesthesia

Succinylcholine should be avoided in patients with muscular dystrophy, especially if onset of symptoms occurred in childhood or adolescence. The possibility of latent or unrecognized DMD in young males (<10 years old) may be a reason to avoid succinylcholine in this patient population. Careful titration of short- or intermediate-duration nondepolarizing **agents** should be done. Reversal **agents** do not appear to be contraindicated.

Upper Motor Neuron Lesions

Patients with hemiplegia or quadriplegia as a result of central nervous system lesions show an abnormal response to both depolarizing and nondepolarizing **agents**. Hyperkalemia and cardiac arrest have been described after succinylcholine, probably as a result of extrajunctional receptor proliferation. Hyperkalemia is typically seen if the drug is given between from 1 week to 6 months after the lesion, but may be seen before and after that period.[34] There is resistance to nondepolarizing **neuromuscular blocking** drugs below the level of the lesion. In hemiplegic patients, monitoring of the affected side

shows that the block is less intense and recovery is more rapid than on the unaffected side. However, the apparently normal

side also demonstrates some resistance to nondepolarizing drugs. Similar findings have been reported after a stroke, with a greater resistance on the affected side.

Burns

As a result of the proliferation of extrajunctional receptors, succinylcholine produces severe hyperkalemia in patients with burns, and this may lead to cardiac arrest. The magnitude of the problem depends on the extent of the injury. It may appear as early as 24 to 48 hours after the burn injury and usually ends with healing.[34] Resistance to the effects of nondepolarizing **neuromuscular blocking agents** is manifest, even in muscles that are apparently not affected by the burn.[49,50]

Miscellaneous

Denervated muscle demonstrates potassium release after succinylcholine and resistance to nondepolarizing relaxants. Contractures in response to succinylcholine have also been observed in amyotrophic lateral sclerosis and multiple sclerosis. There have been isolated reports of hyperkalemia after succinylcholine in several neurologic diseases, including Friedrich's ataxia, polyneuritis, and Parkinson disease.

Monitoring Neuromuscular Blockade

Why Monitor?

Deep levels of paralysis are usually desired during anesthesia to facilitate tracheal intubation and to obtain an immobile surgical field. However, complete return of respiratory function must be attained before the trachea is extubated. Administration of **neuromuscular blocking** drug must be individualized because blockade occurs over a narrow range of receptor occupancy, and because there is considerable interindividual variability in response. Thus, it is important for the clinician to assess the effect of **neuromuscular blocking** drugs without the confounding influence of volatile **agents**, intravenous anesthetics, and opioids. One should remember, however, that monitoring is a tool, not a cure. **Neuromuscular blocking agents** have the same effects, whether or not monitoring is used. Most studies found that monitoring is not associated with a decrease in the incidence of residual paralysis.[9] To test the function of the **neuromuscular** junction, a peripheral nerve is stimulated electrically, and the response of the muscle is assessed.

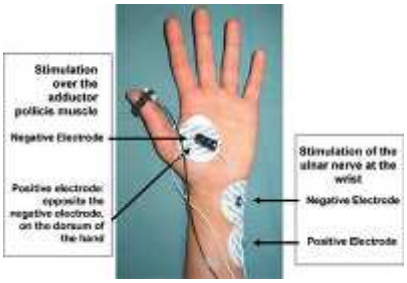

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Figure 20-12. Electrode placement to obtain contraction of the adductor pollicis muscle. The traditional method is to apply the electrodes over the course of the ulnar nerve at the wrist, with the negative electrode distal (*right*). An alternate method is to position the electrodes over the adductor pollicis muscle (*left*), the negative electrode on the palm of the hand, the positive in the same location, but on the dorsum of the hand. The device fixed to the thumb is an accelerometer.

Stimulator Characteristics

The response of the nerve to electrical stimulation depends on three factors: the current applied, the duration of the current, and the position of the electrodes. Stimulators should deliver a maximum current in the range of 60 to 80 mA. Most stimulators are designed to provide constant current, irrespective of impedance changes because of drying of the electrode gel, cooling, decreased sweat gland function, and so forth. However, this constant current feature does not hold for high impedances (>5 kΩ). Thus, electrodes should be firmly applied to the skin. A current display monitor on the stimulator is an asset because accidental disconnection can be identified easily by a current approaching 0 mA. The duration of the current pulse should be long enough for all axons in the nerve to depolarize but short enough to avoid the possibility of exceeding the refractory period of the nerve. In practice, pulse durations of 0.1 to 0.2 msec are acceptable. At least one electrode should be on the skin overlying the nerve to be stimulated. If the negative electrode is used for this purpose, the threshold to supramaximal stimulation is less than for the positive electrode. However, the difference is not large in practice. The position of the other electrode is not critical, but it should not be placed in the vicinity of other nerves. There is no need to use needle electrodes. Silver-silver chloride surface electrodes, used to monitor the electrocardiogram, are adequate for peripheral nerve stimulation, without the risk of bleeding, infection, and burns. In practice, applying these electrodes along the course of a nerve gives the best results (Fig. 20-12).

Monitoring Modalities

Different stimulation modalities were introduced into clinical practice to take advantage of the characteristic features of nondepolarizing **neuromuscular** blockade: fade and posttetanic facilitation with high-frequency stimulation. Thus, the following discussion refers mostly to nondepolarizing block.

Single Twitch

The simplest way to stimulate a nerve is to apply a single stimulus, at intervals of >10 seconds (frequency, <0.1 Hz). This interval is needed to allow the **neuromuscular** junction to recover if nondepolarizing **agents** are used. With shorter intervals, fade might be present. With depolarizing **agents** like succinylcholine, little fade occurs and a higher frequency, such as 1 Hz, may be used without concern for fade. The amplitude of response is compared with a control, preblockade twitch height. The single-twitch modality is useful to construct dose-response curves and to evaluate onset time. However, because a control value is required, the clinical usefulness of this mode of stimulation is limited.

Tetanus

When stimulation is applied at a frequency of ≥30 Hz, the mechanical response of the muscle is fusion of individual twitch responses. In the absence of **neuromuscular blocking** drugs, no fade is present and the response is sustained. During nondepolarizing blockade, the mechanical response appears as a peak, followed by a fade (Fig. 20-9). The sensitivity of tetanic stimulation in the detection of residual **neuromuscular** blockade is greater than that of single twitch; that is, tetanic fade might be present while twitch height is normal. Most nerve stimulators provide a 5-second train at a frequency of 50 Hz. This frequency was adopted because at >100 Hz, some fade may be seen even in the absence of **neuromuscular blocking** drugs. However, more fade is seen with 100-Hz than 50-Hz frequencies, and 100-Hz, 5-second trains are most useful in the detection of residual block.[44,115] With tetanic stimulation, no control prerelaxant response is required, as the degree of muscle paralysis can be assessed by the degree of fade following tetanic stimulation. However, the main disadvantage of this mode of stimulation is posttetanic facilitation (Fig. 20-9), the extent of which depends on the frequency and duration of the tetanic stimulation. For a 50-Hz tetanus applied for 5 seconds, the duration of this interval appears to be at least 1 to 2 minutes.[45] If single-twitch stimulation is performed during that time, the response is spuriously exaggerated.

Train-of-Four

With 2-Hz stimulation, the mechanical or electrical response decreases little after the fourth stimulus, and the degree of fade is similar to that found at 50 Hz.[43] Thus, applying train-of-four stimulation at 2 Hz provides more sensitivity than single twitch and approximately the same sensitivity as tetanic stimulation at 50 Hz. In addition, this relatively low frequency allows the response to be evaluated manually or visually. Moreover, the presence of a small number of impulses (four) eliminates the problem of posttetanic facilitation. Train-of-four stimulation can be repeated every 12 to 15 seconds. There is a fairly close relationship between single-twitch depression and train-of-four response,[116] and no control is required for the latter. During recovery, the second twitch reappears at 80 to 90% single-twitch block, the third at 70 to 80%, and when blockade is 65 to 75%, all four twitches become visible.[117] Then, the train-of-four ratio, the height of the fourth twitch to that of the first twitch, is linearly related to first twitch

height when blockade is <70%. When single-twitch height has recovered to 100%, the train-of-four ratio is approximately 70%.

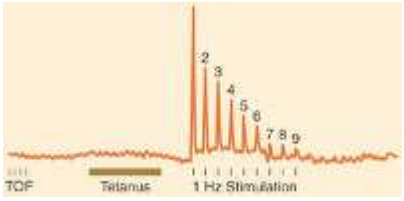

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Figure 20-13. Posttetanic count (PTC). During profound blockade, no response is seen to train-of-four (TOF) or tetanus. However, because there is posttetanic facilitation, some twitches can be seen after tetanic stimulation. In this example, the PTC is 9.

Posttetanic Count

During profound **neuromuscular** blockade, there is no response to single-twitch, tetanic, or train-of-four stimulation. To estimate the time required before the return of a response, one may use a technique that depends on the principle of posttetanic facilitation. A 50-Hz tetanus is applied for 5 seconds, followed by a 3-second pause and by stimulation at 1 Hz. The train-of-four and tetanic responses are undetectable, but facilitation produces a certain number of visible posttetanic twitches (Fig. 20-13). The number of visible twitches correlates inversely with the time required for a return of single-twitch or train-of-four responses.[118] For intermediate-duration drugs, the time from a posttetanic count (PTC) of 1 to reappearance of twitch is 15 to 20 minutes.

Double-Burst Stimulation

Train-of-four fade may be difficult to evaluate by visual or tactile means during recovery from **neuromuscular** blockade. Irrespective of experience, it is difficult for anesthesiologists to detect train-of-four fade when actual train-of-four ratio is 0.4 or greater, meaning that residual paralysis can go undetected.[115] This shortcoming can be overcome, to a certain extent, by applying two short tetanic stimulations (three impulses at 50 Hz, separated by 750 msec), and by evaluating the ratio of the second to the first response. The double-burst stimulation ratio correlates closely with the train-of-four ratio, but is easier to detect manually.[115] At least 12 to 15 seconds must elapse between two consecutive double-burst stimulations.

Recording the Response

Visual and Tactile Evaluation

When electrical stimulation is applied to a nerve, the easiest and least expensive way to assess the response is to observe or feel the response of the muscle. This method is easily adaptable to any

superficial muscle. However, serious errors in assessment can be made. In the case of evaluating the response of the adductor pollicis muscle to ulnar nerve stimulation, the train-of-four count can be made reliably during a surgical procedure,[117] but the quantitative assessment of train-of-four ratio is difficult to make during recovery. Several investigations suggest that train-of-four ratios as low as 0.3[115] can remain undetected.

P.519

The detection rate for tetanic fade (50 Hz) is no better.[115] With double-burst stimulation, fade can be detected reliably up to train-of-four ratios in the range of 0.6 to 0.7.[115] With 100-Hz tetanic stimulation, fade might be detected at train-of-four ratios of 0.8 to 1.0[44,115] and may be seen in individuals with no **neuromuscular** block.

Measurement of Force

A force transducer can overcome the shortcomings of one's senses. If applied correctly, the device provides accurate and reliable responses, displayed as either a digital or an analog signal on a monitor. Force measurement can be measured after single-twitch, tetanus, train-of-four, double-burst, or posttetanic stimulation. However, the availability of tetanus and double-burst stimulation is superfluous if accurate measurement of the train-of-four response can be made. Unfortunately, transducers are expensive, bulky, cumbersome, and can be applied to only one muscle, usually the adductor pollicis.

Electromyography

It is possible to measure the electrical instead of the mechanical response of the muscle. One electrode should be positioned over the **neuromuscular** junction, which is usually close to the midportion of the muscle, and the other near the insertion of the muscle. A third, neutral electrode can be located anywhere else. Theoretically, any superficial muscle can be used for EMG recordings. In practice, such recordings are limited to the hypothenar eminence, the first dorsal interosseous, and the adductor pollicis muscles, which are supplied by the ulnar nerve. Most EMG recording devices compute the area under the EMG curve during a specified time window after the stimulus is applied. There is usually good correlation between EMG and force of the adductor pollicis muscle if the EMG signal is taken from the thenar eminence. The signal obtained from the hypothenar eminence is larger and less subject to movement artifacts, but it can underestimate the degree of paralysis when compared with the adductor pollicis muscle.[119]

Accelerometry

According to Newton's law, acceleration is proportional to force if mass remains unchanged. The device is usually attached to the tip of the thumb (Fig. 20-12) and a digital readout is obtained. The setup is sensitive to inadvertent displacement of the thumb and, in the absence of **neuromuscular blocking** drugs, train-of-four ratios >100% can be obtained.[116] In spite of these shortcomings, accelerometers have become increasingly popular because they are easy to use, are less cumbersome, can be used on muscles

other than the adductor pollicis, and are relatively inexpensive. The use of accelerometry is helpful in the diagnosis of residual paralysis[120] and, in certain circumstances,[121] but not all,[9] it can reduce the incidence of the condition.

Displacement

A variety of devices have been proposed that respond to motion or displacement. They are designed for the adductor pollicis muscle. A thorough evaluation of these devices has not been made, but data indicate that there are slight but clinically insignificant differences between the results such displacement transducers and mechanomyography provide.[122]

Phonomyography

A contracting muscle emits low frequency sounds. Train-of-four response and fade can be heard with a stethoscope placed over the adductor pollicis muscle. A quantitative response can be obtained with special microphones sensitive to frequencies (2 Hz) below the threshold of the human ear. An excellent correlation between phonomyography and force measurement has been found at several muscles, including the adductor pollicis and the corrugator supercilii.[123] At the time of writing, no commercial devices using phonomyography were available.

Choice of Muscle

Muscles do not respond in a uniform fashion to **neuromuscular blocking** drugs. After administration of a **neuromuscular blocking** agent, differences can be measured with respect to onset time, maximum blockade, and duration of action. It is not practical to monitor the muscles of physiological importance, for example, the abdominal muscles during surgery, or the respiratory and upper airway muscles postoperatively. A better approach is to choose a monitoring site that has a response similar to the muscle of interest. For example, monitoring the response of the facial nerve around the eye is a good indicator of intubating conditions, and the use of the adductor pollicis muscle during recovery reflects upper airway muscle function. Another strategy is to stick to one monitoring site, such as the adductor pollicis muscle, and interpret the information provided from knowledge of the different responses between muscles (Fig. 20-14).

Adductor Pollicis Muscle

The adductor pollicis muscle is accessible during most surgical procedures. It is supplied by the ulnar nerve, which becomes superficial at the wrist where a negative electrode can be positioned. The positive electrode is applied a few centimeters proximally (Fig. 20-12). The force of contraction of the adductor pollicis muscle can be measured easily, and it has become a standard in research. After injection of a dose that produces less than 100% blockade, the time to maximal blockade is longer than in centrally located muscles.[124,125] The adductor pollicis muscle is relatively sensitive to nondepolarizing **neuromuscular blocking** drugs, and during recovery it is blocked more than some respiratory muscles such as the diaphragm,[124] laryngeal adductors,[125] and abdominal muscles (Fig. 20-14).[126] There is evidence

that recovery of the adductor pollicis and of upper airway muscles occurs more or less simultaneously (Fig. 20-14).[127]

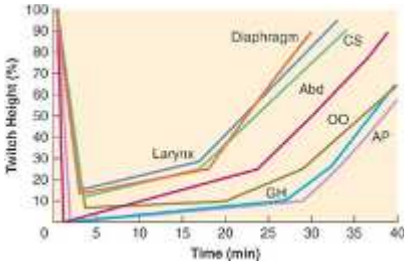

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Figure 20-14. Approximate time course of twitch height after rocuronium, 0.6 mg/kg, at different muscles. Diaphragm, diaphragm; larynx, laryngeal adductors (vocal cords); CS, corrugator supercilii muscle (eyebrow); Abd, abdominal muscles; OO, orbicularis oculi muscle (eyelid); GH, geniohyoid muscle (upper airway); AP, adductor pollicis muscle (thumb). (Data are taken or inferred from references 75, 126, 127, and 129.)

The adductor pollicis muscle can also be stimulated by applying electrodes directly over it. This can be accomplished by placing the two electrodes in the space lying between the base of the first and second metacarpals, on the palmar and dorsal aspects on the hand, respectively (Fig. 20-12). Such a stimulation avoids the confounding movement of hypothenar muscles. Direct muscle stimulation with this electrode position does not normally occur because **neuromuscular blocking agents** abolish the response completely.[128] The ability to detect fade by visual or tactile means is the same, whether the stimulating electrodes are applied at the wrist or the hand.[115]

Other Muscles of the Hand

Ulnar nerve stimulation also produces flexion and abduction of the fifth finger, which usually recovers before the adductor pollicis muscle, the discrepancy in first twitch or train-of-four ratio being of the order of 15 to 20%.[119] Relying on the response of the fifth finger might overestimate recovery from blockade. Abduction of the index finger also results from stimulation of the ulnar nerve because of contraction of the first dorsal interosseous, the sensitivity of which is comparable with that of the adductor pollicis muscle. The hypothenar eminence (near the fifth finger) and the first dorsal interosseous are particularly well suited for EMG recordings.[119] Stimulation in the hand (Fig. 20-12) eliminates contraction of the hypothenar muscles, but may evoke movement of the first dorsal interosseous.

Muscles Surrounding the Eye

There seem to be major differences in the response of muscles innervated by the facial nerve and located around the eye, and these differences have introduced some confusion in the literature. The orbicularis

oculi muscle essentially covers the eyelid, and its response to **neuromuscular blocking agents** is similar to that of the adductor pollicis muscle.[129] However, it is customary to observe the movement of the eyebrow, and recordings at that site are similar to that of the laryngeal adductors (Fig. 20-14).[129] Onset of blockade is more rapid and recovery occurs sooner than at the adductor pollicis. Thus, facial nerve stimulation with inspection of the response of the eyebrow (which most likely represents the effect of the corrugator supercilii, not the orbicularis oculi muscle) is indicated to predict intubating conditions and to monitor profound blockade. The facial nerve can be stimulated 2 to 3 cm posterior to the lateral border of the orbit. There is no need to use stimulating currents >20 to 30 mA.

Muscles of the Foot

The posterior tibial nerve can be stimulated behind the internal malleolus to produce flexion of the big toe by contraction of the flexor hallucis muscle. The response of this muscle is comparable with that of the adductor pollicis muscle. Stimulation of the external peroneal nerve produces dorsiflexion, but the sensitivity of the muscles involved has not been measured.

Clinical Applications

Monitoring Onset

The quality of intubating conditions depends chiefly on the state of relaxation of muscles of the jaw, pharynx, larynx, and respiratory system. Onset of action is faster in all these muscles than in the hand or foot because they are closer to the central circulation and they receive a greater blood flow. Among these central muscles, the diaphragm and especially the laryngeal adductors are the most resistant to nondepolarizing **agents**. The diaphragm is an important muscle because its blockade prevents coughing, and if laryngeal muscles are paralyzed, vocal cords are relaxed, allowing easy passage of a tracheal tube. The relationship between onset time in laryngeal and hand muscles depends on dose. At relatively low doses (e.g., rocuronium, 0.3 to 0.4 mg/kg), onset time is slower at the adductor pollicis than at the laryngeal muscles. If the dose is increased (e.g., rocuronium, 0.6 to 1.0 mg/kg), onset is faster at the adductor pollicis muscle because these doses produce 100% blockade at the adductor pollicis without **blocking** laryngeal muscles completely (Fig. 20-14).[73] Onset time decreases considerably in any muscle if the dose given is sufficient to reach 100%. Finally, if the dose is large enough to block the laryngeal muscles completely, onset time again becomes shorter at the larynx. It is not surprising that monitoring the adductor pollicis muscle predicts intubating conditions poorly. Facial nerve stimulation with visual observation of the response over the eyebrow gives better results because the response of the corrugator supercilii is close to that of the vocal cords. Train-of-four fade takes longer to develop than single-twitch depression (Fig. 20-9), and during onset, train-of-four stimulation does not have any advantages over single-twitch stimulation at 0.1 Hz.

Monitoring Surgical Relaxation

Adequate surgical relaxation is usually obtained when fewer than two or three visible twitches are observed at the adductor pollicis muscle. However, this criterion might prove inadequate in certain

circumstances when profound relaxation is required owing to the discrepancy between the adductor pollicis and other muscles. In this case, the PTC can be used at the adductor pollicis muscle,[118] provided that this type of stimulation is not repeated more often than every 2 to 3 minutes. A suitable alternative is stimulation of the facial nerve with observation of the response over the eyebrow, which recovers at the same rate as such resistant muscles as the diaphragm.[124,129]

Monitoring Recovery

Complete return of **neuromuscular** function should be achieved at the conclusion of surgery unless mechanical ventilation is planned. Thus, monitoring is useful in determining whether spontaneous recovery has progressed to a degree that allows reversal **agents** to be given and to assess the effect of these **agents**.

The effectiveness of anticholinesterase **agents** depends directly on the degree of recovery present when they are administered. Preferably, reversal **agents** should be given only when four twitches are visible at the adductor pollicis muscle,[130] which corresponds to a first-twitch recovery of >25%. The presence of spontaneous breathing is not a sign of adequate **neuromuscular** recovery. The diaphragm recovers earlier than the much more sensitive upper airway muscles, such as the geniohyoid, which recovers, on average, at the same time as the adductor pollicis muscle.[127] To prevent upper airway obstruction after extubation, it is preferable to use the adductor pollicis muscle to monitor recovery, instead of the more resistant muscles of the hypothenar eminence or those around the eye.

Finally, the adequacy of recovery should be assessed. Traditionally, a train-of-four ratio of 0.7 was considered to be the threshold below which residual weakness of the respiratory muscles could be present. There is abundant evidence that significant weakness may occur up to train-of-four ratio values of 0.9.[10,123] Awake volunteers given mivacurium failed to perform the head-lift test when the train-of-four ratio at the adductor pollicis muscle decreased below 0.62, but needed a train-of-four ratio of at least 0.86 to hold a tongue depressor

between their teeth (Fig. 20-15).[131] This suggests that the head-lift test does not guarantee full recovery, and that the upper airway muscles used to retain a tongue depressor are very sensitive to the residual effects of **neuromuscular blocking** drugs. Furthermore, impairment in swallowing and laryngeal aspiration of a pharyngeal fluid was observed at train-of-four ratios as high as 0.9 in volunteers given vecuronium (Fig. 20-4).[132]

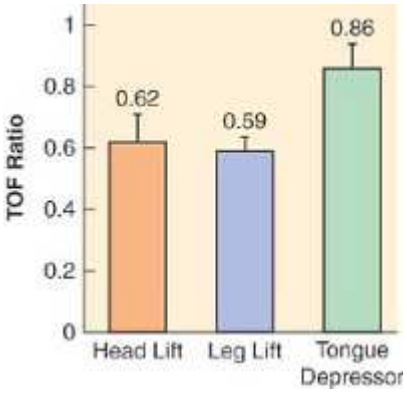

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Figure 20-15. Correlation between train-of-four (TOF) responses at the adductor pollicis muscle and certain clinical tests of **neuromuscular** recovery. Volunteers were given mivacurium and were asked to lift their heads for 5 seconds (head lift), lift their legs for 5 seconds (leg lift), or hold a tongue depressor between their teeth against force (tongue depressor). The minimum TOF ratio (and SD) when each of these tests was passed is indicated. (Data from Kopman et al.[131])

Anesthetized patients appear considerably more sensitive to the ventilatory effects of **neuromuscular blocking** drugs than are awake patients. Whereas tidal volume and end-tidal CO_2 are preserved in awake patients receiving relatively high doses of **neuromuscular blocking** drugs,[133] anesthetized adults have a decreased tidal volume and increased PCO_2 with doses of pancuronium as low as 0.5 mg.[134] In conscious volunteers, administration of small doses of vecuronium to maintain train-of-four at <0.9 leads to severe impairment of the ventilatory response to hypoxia (Fig. 20-16).[135] The response to hypercapnia is maintained, and this indicates that the response to hypoxia is not a result of respiratory muscle weakness.[135]

Taken together, the results of these investigations indicate that normal respiratory and upper airway function does not return to normal unless the train-of-four ratio at the adductor pollicis muscle is 0.9 or more. However, it has become apparent that human senses fail to detect either a train-of-four or 50-Hz tetanic fade when the train-of-four ratio is as low as 0.3.[115] With double-burst stimulation, detection failures may occur at train-of-four ratios of 0.6 to 0.7.[115] Compared with the train-of-four, the ability to detect fade is not improved by using tetanic stimulation at 50 Hz for 5 seconds. However, fade can be detected visually at train-of-four ratios of 0.8 to 0.9 by using 100-Hz tetanic stimulation,[46,115] although this threshold may vary from patient to patient.[115] Because of the presence of posttetanic facilitation, 50- or 100-Hz stimuli should not be applied more often than every 2 minutes. Because of the limitations of one's senses, it has been advocated that quantitative assessment of the train-of-four ratio be made routinely.[10] Mechanographic and EMG equipment give reliable values of train-of-four ratio, but the use of this equipment is limited by size, cost, and convenience. Accelerometers are less bulky and cheaper, but they can overestimate the value of train-of-four ratio during recovery.[116] It has been suggested that a train-of-four ratio of 1.0 obtained by accelerometry must be obtained before **neuromuscular** function can be considered complete.[115] Monitoring devices based on the measurement of displacement or sound may prove to have more reliable train-of-four ratios than accelerometry. In one study, a transmission module

sensitive to bending and deformation was found to yield train-of-four ratio values comparable to mechanomyography during the recovery period.[122]

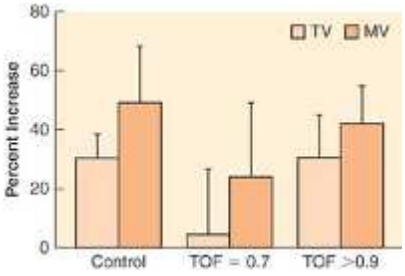

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Figure 20-16. Response to hypoxia is impaired during recovery from vecuronium blockade. Normal response is an increase in minute volume (MV) or tidal volume (TV; control). These increases are decreased significantly when vecuronium produces a train-of-four ratio (TOF) of 0.7 at the adductor pollicis muscle. They return to near-normal values at a TOF >0.9. (Data from Eriksson et al.[135])

In response to the shortcomings of visual or tactile evaluations, another approach to recovery is to wait until sufficient spontaneous recovery is present and give reversal **agents** systematically. If given at a train-of-four count of 2 during cisatracurium or rocuronium blockade, complete recovery is not achieved until 15 minutes or so later, with some patients still having train-of-four ratios <0.9 after 30 minutes.[136] Thus, the recommendation is to wait until all four twitches have reappeared. In any event, clinicians must be aware of the limitations of the tests they are using and complete their evaluations with clinical tests.

Factors Affecting the Monitoring of Neuromuscular Blockade

Many drugs interfere with **neuromuscular** function and these are dealt with elsewhere (see "Drug Interactions"). However, certain situations make the interpretation of data on **neuromuscular** function difficult. Central hypothermia may slow the metabolism of **neuromuscular blocking agents** and prolong blockade in all muscles of the body.[137] If the extremity where monitoring is performed is cold, the degree of block will be accentuated. Thus, if only the monitored hand is cold, without central hypothermia, the degree of paralysis will appear to be increased.[137] Resistance to nondepolarizing **neuromuscular blocking** drugs occurs with nerve damage, including peripheral nerve trauma, cord transection, and stroke. In this case, monitoring of the involved limb would tend to underestimate the degree of muscle paralysis. The level of paralysis should also be adjusted for the type of patient, as well as the type of surgery. For example, it is not necessary to paralyze frail individuals or patients at the extremes of age to the same extent as young muscular adults. The same applies to patients with debilitating muscular diseases. **Neuromuscular** monitoring by itself does not guarantee adequate relaxation during surgery and complete recovery postoperatively. The surgical field may be poor in spite of full paralysis of the hand because of difference in response between muscles. For example, evidence of breathing efforts can be manifest on the expired CO_2 curve when no twitch is present at the adductor pollicis muscle following ulnar

nerve stimulation, reflecting the earlier recovery of the diaphragm.[124,126] Residual paralysis might occur because of excess neuromuscular blocking agents given, early administration of reversal, or an abnormal response of the patient. The effect of the neuromuscular blocking drug is the same whether or not monitoring is used. Neuromuscular monitoring can help in the diagnosis of inadequate skeletal muscle relaxation during surgery or insufficient recovery after surgery, but does not, in itself, treat these conditions.[9]

Antagonism of Neuromuscular Block

In most circumstances, all efforts should be made to ensure that the patient leaves the operating room with unimpaired muscle strength. Specifically, respiratory and upper airway muscles must function normally so the patient can breathe, cough, swallow secretions, and keep his or her airway patent. Two strategies can be adopted to achieve this goal. The first is to titrate neuromuscular blocking agents carefully so that no residual effect is manifest at the end of surgery. The second is to accelerate recovery by giving a reversal drug. This second option is probably safer, but both strategies require careful assessment of blockade. A third possibility that might be available in the near future is selective binding of neuromuscular blocking agents with a cyclodextrin molecule to restore neuromuscular function.

Assessment of Neuromuscular Blockade

Spontaneous breathing can resume even if relatively deep degrees of paralysis are still present because of the relative diaphragm-sparing effect of neuromuscular blocking agents. Spontaneous ventilation, adequate to prevent hypercapnia, can be maintained despite considerable measurable skeletal muscle weakness if a patent airway is ensured. The ability to perform maneuvers such as vital capacity, maximum voluntary ventilation, and forced expiratory flow rate recovers at less intense levels of paralysis because it requires a greater strength.[133] However, such tests are difficult to perform in everyday practice, particularly when the patient is recovering from general anesthesia. Moreover, the weakest point in the respiratory system is the upper airway. When given vecuronium, swallowing was impaired and laryngeal aspiration occurred when the train-of-four ratio was ≤0.9.[132] These problems are difficult to diagnose when a tracheal tube is in place. Consequently, several indirect indices, which are easier to measure, have been correlated with the more specific tests of lung and upper airway function.

Clinical Evaluation

Several crude tests have been suggested, including head lift for 5 seconds, tongue protrusion, and the ability to lift the legs off the bed to determine recovery of neuromuscular function. Pavlin et al.[133] correlated the maximum inspiratory pressure with tests of skeletal muscle strength and of airway musculature in conscious volunteers receiving *d*-tubocurarine. As the dose was increased, head lift and leg raising were affected first. Then, the ability to swallow, touch teeth, and maintain a patent airway was impaired. At that time, hand grip strength was decreased markedly. Nevertheless, as long as the

mandible was elevated by an observer, end-tidal CO_2 was normal even when the subject failed all other tests. From these data, Eriksson et al.[132] concluded that ability to maintain head lift for 5 seconds usually indicates sufficient strength to protect the airway and support ventilation. However, Kopman et al.[131] have shown, in volunteers, that the most sensitive test is the ability to clamp the jaws shut and prevent removal of a tongue depressor. This maneuver correlated with a train-of-four ratio measured at the adductor pollicis muscle of >0.86, whereas head lift and leg lift could be performed at more intense levels of paralysis (train-of-four approximately 0.6; Fig. 20-15). All subjects complained of visual symptoms until train-of-four was >0.9. Pressure measurements in the upper esophagus have been shown to be decreased (Fig. 20-4) and laryngeal aspiration detected at a train-of-four ratio <0.9.[132] Thus, it appears that a normal head lift or leg lift is insufficient to guarantee normal upper airway function. The ability to resist removal of an object (such as a tongue depressor or a tracheal tube) from the mouth by closing the teeth probably correlates better with adequate upper airway function.

Evoked Responses to Nerve Stimulation

The clinical tests previously described are usually unobtainable in the patient recovering from anesthesia. Furthermore, it is preferable to assess the degree of recovery before emergence. Evoked responses to nerve stimulation are then appropriate. The target is a train-of-four >0.9, considering that upper airway function does not recover completely until the train-of-four ratio at the adductor pollicis muscle is at least 0.9.

With the introduction of short- and intermediate-duration nondepolarizing **agents** into clinical practice, the use of reversal **agents** has been considered by some as optional. The decision to omit pharmacologic reversal of **neuromuscular** blockade must be made carefully because the presence of residual paralysis may be missed. As mentioned earlier, manual and tactile evaluation of **neuromuscular** blockade by train-of-four or 50-Hz tetanic stimulation may fail to detect fade.[115] Double-burst stimulation is more sensitive, but becomes unreliable at train-of-four ratios in the range of 0.6 to 0.9.[115] The most sensitive test is the ability to maintain sustained contraction to 100-Hz tetanus for 5 seconds. Fade may be detected when train-of-four ratio is as high as 0.8 to 0.9.[46,115] Tetanic stimulation at 100 Hz is painful and must be performed only in adequately anesthetized patients.

Because of the limitations of the visual and tactile estimate of the train-of-four response during recovery, objective measurement has been advocated.[10] Acceleromyographic recordings might be the most practical because accelerometers are cheap and easy to use. However, it must be appreciated that the train-of-four ratio obtained with accelerometry is greater than that measured with mechanomyography and may exceed 1.0. An accelerographic train-of-four ratio of 1.0 has been proposed as the equivalent of a mechanomyographic train-of-four of 0.9.[115]

Residual Paralysis

Several studies have demonstrated that residual **neuromuscular** blockade is frequent in patients in the recovery room after surgery. Viby-Mogensen et al.[138] found in 72 adult patients given long-acting **agents**

that the train-of-four ratio was 0.7 in 30 (42%) patients, and that 16 of the 68 patients (24%) who were awake were unable to sustain head lift for 5 seconds. In that study, the patients received appropriate doses of neostigmine. Similar results have been obtained in other parts of the world (Table 20-1).[9,139] The incidence of train-of-four ratio 0.7 is reduced from about 30% to <10% if the intermediate agents atracurium or vecuronium are substituted for the long-acting drugs and if reversal is given.[9,139,140] However, the actual incidence of residual paralysis was certainly underestimated in the earlier studies because of the criterion used (train-of-four ratio of 0.7).

Recently, there has been a trend for a greater incidence of residual paralysis, even with intermediate-duration drugs. This can be explained by two factors. The threshold for residual paralysis has been raised from a train-of-four ratio of 0.7 to 0.8 and then to 0.9.[9] However, the most important reason for high incidence of residual paralysis seems to be omission of reversal. In one study, more systematic institution of pharmacologic reversal was associated with a decrease in the incidence of residual paralysis (train-of-four >0.9) from 62% to 3%.[141]

Clinical Importance

Residual paralysis in the recovery room has been shown to be associated with significant morbidity. In 1997, Berg et al.[140] studied nearly 700 general surgical patients who randomly received pancuronium, vecuronium, or atracurium to produce surgical relaxation. In patients who had received pancuronium, the incidence of postoperative partial paralysis, defined by the then-accepted criterion of a train-of-four ratio <0.7, was 5 times that in patients receiving either of the two intermediate-acting drugs (26 vs. 5%). In addition, the incidence of atelectasis demonstrated on chest radiographs taken 2 days later was greater in patients who had received pancuronium and who had not attained a train-of-four ratio of 0.7 (16%) than in those who exceeded this threshold (4.8%).[140] Intense residual block has been demonstrated in patients after cardiac surgery, especially if pancuronium was chosen over rocuronium.[66]

Reversal Agents

So far, the only compounds that have been widely used to reverse the effect of neuromuscular blocking agents are the anticholinesterase drugs. The pharmacologic principle involved is inhibition of acetylcholine breakdown to increase its concentration of acetylcholine at the neuromuscular junction, thus tilting the competition for receptors in favor of the neurotransmitter.[139] Other drugs such as suramin and 3–4 aminopyridine are not as effective, or more toxic, or both. The monopoly occupied by anticholinesterase agents might be challenged soon with the introduction of a selective binding agent, sugammadex, which is now undergoing clinical trials in North America and Europe.

Anticholinesterases: Mechanism of Action

Neostigmine, edrophonium, and pyridostigmine inhibit acetylcholinesterase, but this may not be the only mechanism by which blockade is antagonized. This inhibition is present at all cholinergic synapses in the peripheral nervous system. Thus, the anticholinesterases have potent parasympathomimetic activity, which is attenuated or abolished by the administration of an antimuscarinic agent, atropine or glycopyrrolate. Neostigmine, edrophonium, and pyridostigmine are quaternary ammonium compounds, which do not penetrate the blood–brain barrier well. Thus, although these **agents** have the ability to affect cholinergic function in the central nervous system, the concentrations in the brain are usually too small for such an effect. Physostigmine is an anticholinesterase that can cross the blood–brain barrier easily. For this reason, it is not used to reverse **neuromuscular** blockade.

Neostigmine and pyridostigmine are attached to the anionic and esteratic sites of the acetylcholinesterase molecule and produce longer lasting inhibition than edrophonium. Neostigmine and pyridostigmine are inactivated by the interaction with the enzyme, whereas edrophonium is unaffected.[139] Inhibition of acetylcholinesterase results in an increased amount of acetylcholine reaching the receptor and in a longer time for acetylcholine to remain in the synaptic cleft. This causes an increase in the size and duration of the end plate potentials.[142] There is evidence that some of the effects of neostigmine are not the result of cholinesterase inhibition.[142]

Anticholinesterases also have presynaptic effects. In the absence of **neuromuscular blocking** drugs, they potentiate the normal twitch response in a way similar to succinylcholine, probably as a result of the generation of action potentials that spread antidromically. A ceiling effect, that is, the inability for large doses to produce an increasing effect, has been demonstrated in vitro[143] and can be observed in patients.[144]

Neostigmine Block

Large doses of anticholinesterases, especially if given when **neuromuscular** block is absent, may produce evidence of **neuromuscular** dysfunction. For example, dose-dependent decreases in the EMG activity of the genioglossus and the diaphragm have been measured following neostigmine administration in rats.[145] The problem might be less when some degree of **neuromuscular** blockade is present before neostigmine is given. The mechanism involved is uncertain. There are no clinical reports of postoperative weakness attributed to reversal **agents**. Still, it appears prudent to reduce the dose of anticholinesterase agent if recovery from **neuromuscular** block is almost complete.

Potency

Dose-response curves have been constructed for edrophonium, neostigmine, and pyridostigmine. During a constant infusion of **neuromuscular blocking** drugs, the curves are obtained by plotting the peak effect versus the dose of reversal agent. In this situation, neostigmine was found to be approximately 12 times as potent as edrophonium.[146] However, the curves are not parallel, that of edrophonium being flatter. This indicates that edrophonium is effective over a narrower range of blockade and less effective against deep blockade. This was verified when neostigmine and edrophonium were used to reverse atracurium

blockade. More neostigmine and edrophonium were required to reverse deep (99%) than moderate (90%) block, but the difference was greater for edrophonium.[147] There is no difference in the dose-response relationship of anticholinesterases if vecuronium is infused instead of pancuronium, but there is a marked shift to the left for the curves obtained during vecuronium block if the reversal agent is given during spontaneous recovery.[148] This indicates that anticholinesterase-assisted recovery is the sum of two components: (1) spontaneous recovery from the **neuromuscular blocking** agent itself, which depends on the pharmacokinetic characteristics of the drug, and (2) assisted recovery, which is a function of the dose and type of anticholinesterase agent given.

Pharmacokinetics

Following bolus intravenous injection, the plasma concentration of the anticholinesterases decreases rapidly during the first 5 to 10 minutes and then more slowly.[139] Volumes of distribution are in the range of 0.7 to 1.4 L/kg and the elimination half-life is 60 to 120 minutes. The drugs are water-soluble, ionized compounds so that their principal route of excretion is the kidney. Their clearances are in the range of 8 to 16 mL/kg/min, which is much greater than the glomerular filtration rate because they are actively secreted into the tubular lumen. Their clearance is reduced markedly in patients in renal failure.

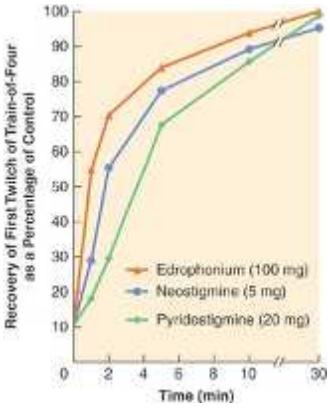

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Figure 20-17. Reversal of pancuronium blockade at 10% twitch recovery. Reversal is given at time zero. Edrophonium is faster then neostigmine, which is faster than pyridostigmine. (Redrawn from Ferguson A, Egerszegi P, Bevan DR: Neostigmine, pyridostigmine, and edrophonium as antagonists of pancuronium. Anesthesiology 1980; 53: 390.)

Pharmacodynamics

The onset of action of edrophonium (1 to 2 minutes) to peak effect is much more rapid than that of neostigmine (7 to 11 minutes) or pyridostigmine (15 to 20 minutes; Fig. 20-17).[162] The reason for the differences is uncertain, but may be related to the different rates of binding to the enzyme. The duration of action (1 to 2 hours) is similar to their elimination half-life. Even when used to reverse blockade produced by long-acting **agents**, duration of action of anticholinesterase **agents** is comparable with or

most often exceeds that of the neuromuscular blocking drug. Well-documented recurarization has not been reported. In practice, cases of apparent reparalysis in the recovery room are incomplete reversal that was initially thought to be complete. Either manual or visual assessment is performed using the train-of-four or tetanus mode, which can yield to gross underevaluation of residual paralysis, or respiratory function appeared adequate when the tracheal tube is in place, but once extubated, the patient cannot maintain a patent airway.

Factors Affecting Reversal

Several factors modify the rate of recovery of neuromuscular activity after reversal.

Intensity of Block

The more intense the block at the time of reversal, the longer the recovery of neuromuscular activity (Fig. 20-18).[144] In addition, neostigmine is more effective than edrophonium or pyridostigmine in antagonizing intense (90%) blockade. When reversal is administered after spontaneous recovery to ≥25% T_1 has occurred, recovery is rapid and the time from reversal to train-of-four >0.9 is usually only a few minutes, although recovery after pancuronium may not be complete.[68] Thus, Kopman et al.[136] recommended that reversal should not be attempted until T_1 ≥25% when four twitches to train-of-four stimulation are visible. Attempted reversal at only two twitches may take 30 minutes or more to reach train-of-four of 0.9.

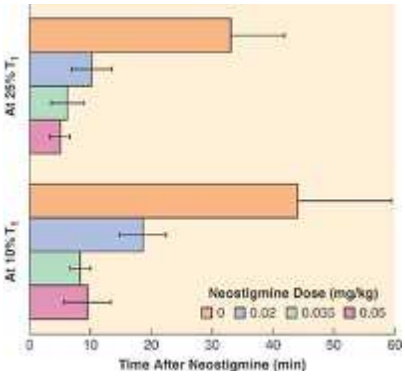

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Figure 20-18. Neostigmine is more effective at greater degree of recovery from rocuronium blockade. Time to reach a train-of-four ratio of 0.8 after various doses of neostigmine. This time is less if neostigmine is given at 25% than at 10% first-twitch recovery. Notice a ceiling effect for neostigmine at doses >0.035 mg/kg. A dose of 0 indicates no reversal given. (Data from McCourt et al.[144])

One might argue that reversal can be attempted earlier, for instance when there is only one or no twitch visible following train-of-four stimulation, because one would otherwise spend time waiting for all four twitches to reappear. Several studies dealt with the problem of total time between injection of the neuromuscular blocking agent until complete recovery, with the reversal agent given at different levels of spontaneous recovery. Bevan et al.[148] administered large doses of neostigmine (0.07 mg/kg) after rocuronium and vecuronium and measured time until train-of-four ratio was 0.9. Neostigmine decreased the time to recovery, no matter when it was given. However, time from injection to full reversal was not

less when neostigmine was given 5 minutes after rocuronium (42.1 minutes) than at 25% recovery (28.2 minutes; Fig. 20-19).[148] In addition, giving the reversal agent too early leads to a period of "blind paralysis" because neostigmine-assisted recovery is characterized by an early, rapid phase, followed by slower recovery. As a result, the interval between a train-of-four ratio of 0.4 to 0.9, that is, the time when fade is difficult to detect, is likely to be much longer with early neostigmine administration. Thus, there is little advantage in attempting early reversal.

Dose

Over a certain dose range, the degree and rate of reversal depends directly on dose.[144,147] However, all anticholinesterase agents demonstrate a ceiling effect (Fig. 20-18). Usually, there is no added benefit in giving doses exceeding 0.07 mg/kg neostigmine, or 1.0 mg/kg edrophonium.

Choice of Neuromuscular Blocking Agent

Recovery of neuromuscular activity after reversal depends on the rate of spontaneous recovery as well as the acceleration induced by the reversal agent. Consequently, the overall recovery of intermediate-acting agents (atracurium, vecuronium, mivacurium, rocuronium) following the same dose of anticholinesterase is more rapid and more complete than after pancuronium,

d-tubocurarine, or gallamine.[68] This difference is probably why residual paralysis is more frequent with longer-acting neuromuscular blocking agents. After prolonged infusions, recovery is slower than after intermittent bolus administration.

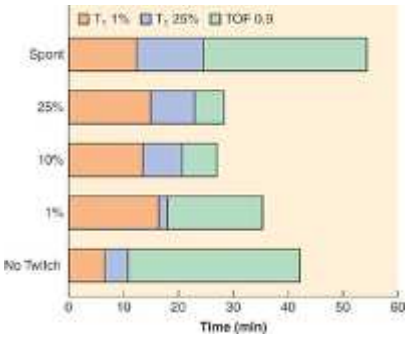

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Figure 20-19. Time from injection of rocuronium until recovery to train-of-four ratio (TOF) of 0.9 in adults. Reversal with neostigmine was either not given (Spont) or given at 25%, 10%, or 1% twitch recovery, or given 5 minutes after rocuronium, when there was no twitch. Times from rocuronium injection to 1% first twitch, 25% first twitch, and TOF of 0.9 are indicated. Neostigmine was optimal when given at 10 to 25%. Giving it early had no advantage. (Data from Bevan et al.[148])

Age

Recovery of neuromuscular activity occurs more rapidly with smaller doses of anticholinesterases in infants and children than in adults (Fig. 20-20).[148] Residual weakness in the recovery room is found less frequently in children than in adults. The effectiveness of reversal has not been studied extensively in the

elderly. Although the elimination of anticholinesterases is reduced in this age group, this reduction is counterbalanced by the tendency for neuromuscular blockade to wear off more slowly. This is especially true of steroidal neuromuscular blocking agents, such as vecuronium and rocuronium, which have a slower recovery index in the elderly.

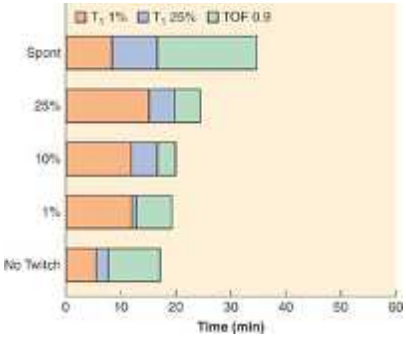

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Figure 20-20. Same graph as in Figure 20-19, but in children 2 to 12 years old. Spontaneous recovery from rocuronium blockade (Spont) is more rapid, as well as neostigmine-assisted recovery. (Data from Bevan et al.[148])

Drug Interactions

Drugs that potentiate neuromuscular blockade can slow reversal or produce recurarization if given after anticholinesterase administration. Halogenated agents, when continued after neostigmine administration, prolong time to full reversal. Even when they are discontinued at the time of anticholinesterase drug administration, reversal time is not reduced significantly, probably because washout of the vapor from muscle tissue takes time. Care must be taken if aminoglycoside antibiotics or magnesium must be given shortly after reversal agents.

Renal Failure

Anticholinesterases are actively secreted into the tubular lumen so that their clearance is reduced in renal failure.[139] Thus, duration of action of neostigmine and edrophonium is increased in renal failure, at least to a comparable extent as duration of action of the neuromuscular blocking agent. No cases of recurarization have been reported.

Anticholinesterases: Other Effects

Cardiovascular

Anticholinesterases provoke profound vagal stimulation. The time course of the vagal effects parallels the reversal of block, which is rapid for edrophonium and slower for neostigmine. However, the bradycardia and bradyarrhythmias can be prevented with anticholinergic agents. Atropine has a rapid onset of action (1 minute), duration of 30 to 60 minutes, and crosses the blood-brain barrier. Its time course makes it appropriate for use in combination with edrophonium,[146] whereas glycopyrrolate (onset 2 to 3 minutes) is more suitable with neostigmine or pyridostigmine. Because glycopyrrolate does not cross the blood-brain

barrier, it is believed that the incidence of memory deficits after anesthesia is less than that after atropine. If atropine is given with neostigmine, the dose is approximately half that of neostigmine (atropine 20 μg/kg for neostigmine 40 μg/kg). Such a combination leads to an initial tachycardia followed by a slight bradycardia. With glycopyrrolate, the dose is one-fourth to one-fifth that of neostigmine. Atropine requirements are less with edrophonium than with neostigmine (atropine 7 to 10 μg/kg with edrophonium 0.5 mg/kg).

Other Cholinergic Effects

Anticholinesterases produce increased salivation and bowel motility. Although atropine blocks the former, it appears to have little effect on peristalsis. Some reports claim an increase in bowel anastomotic leakage after the reversal of **neuromuscular** blockade. There has been concern over the possible impact of anticholinesterase **agents** on postoperative nausea and vomiting (PONV). A meta-analysis, published in 1999, concluded that neostigmine had no effect on the overall incidence of PONV, but large doses (2.5 mg or more in adults) was associated with a higher incidence of PONV than no reversal, while lower doses led to less PONV.[149] A more recent meta-analysis reanalyzed the data and incorporated additional studies. It concluded that there was no relation between administration

of neostigmine and PONV.[150] At any rate, possible nausea and vomiting is preferable to signs and symptoms of respiratory paralysis.

Respiratory Effects

Anticholinesterases may cause an increase in airway resistance, but anticholinergics reduce this effect. Several other factors, such as pain, the presence of an endotracheal tube, or light anesthesia, may predispose to bronchoconstriction at the end of surgery so that it is difficult to incriminate the reversal **agents**.

Clinical Use

Several strategies have been proposed to restore **neuromuscular** function at the end of surgery and anesthesia. One of them involves restricting the dose of nondepolarizing **blocking** agent at induction of anesthesia to what is necessary for the duration of the procedure, minimal additional doses and reliance of complete spontaneous recovery in an attempt to avoid reversal with anticholinesterase **agents**. This approach is not without dangers. Even relatively modest doses ($2 \times ED_{95}$) of atracurium, vecuronium, or rocuronium are associated with residual paralysis (train-of-four ratio <0.9) after as long as 4 hours after injection.[120] Visual or tactile monitoring with train-of-four, 50 Hz-tetanus, or double-burst stimulation stimulation cannot rule out some degree of residual paralysis.[115] Only a sustained response to a 100-Hz tetanus may rule out the presence of residual paralysis by tactile or visual means.[44,115] The use of objective monitoring, such as acceleromyography, is even better.[115] Still, pharmacologically assisted recovery is expected in most cases, as it is illusory to aim for complete recovery only by careful titration of

neuromuscular blocking agents. In a study examining anesthetic outcomes in The Netherlands, the use of reversal **agents** was found to be associated with a tenfold reduction in mortality.[151] Not surprisingly, the more systematic use of reversal **agents** in one institution led to a substantial decrease in residual paralysis.[141]

Administration of anticholinesterase **agents** will accelerate recovery, no matter when they are given in the course of recovery (Fig. 20-19). However, there are advantages in giving reversal **agents** when spontaneous recovery is well under way, preferably when four twitches are present after train-of-four stimulation. If neostigmine is given when deep blockade is present (no twitch or only one twitch present; Figs. 20-18 and 20-19), reversal takes longer than if four twitches are present. As a result, time from injection of rocuronium until full recovery (train-of-four >0.9) is not reduced, and my in fact be increased, if neostigmine is given too early (Fig. 20-19). Furthermore, the patient might be more difficult to manage with early reversal: duration of blind paralysis (from train-of-four of 0.4, when train-of-four fade becomes undetectable, until train-of-four is 0.9) is longer with early reversal. This means that missing residual paralysis is more likely with hasty administration of anticholinesterase **agents**. Therefore, if four twitches are not visible after train-of-four stimulation, it is recommended to keep the patient anesthetized and mechanically ventilated until four twitches reappear and then administer anticholinesterases.

Intense blockade is not expected to be reversed effectively by increasing the dose of anticholinesterase (Fig. 20-18). In general, neostigmine doses of 0.04 to 0.05 mg/kg should be sufficient, and there is no advantage in exceeding 0.07 mg/kg because of the ceiling effect of the drug. Edrophonium is not recommended for intense block. Pyridostigmine has a slow onset of action and does not appear to accelerate reversal of short- and intermediate-duration drugs to a great extent.

When recovery appears almost complete—that is, when four seemingly equal twitches are seen after train-of-four stimulation—a reduced dose of neostigmine (0.015 to 0.02 mg) is probably adequate. In this situation, edrophonium (0.2 to 0.5 mg/kg) may also be given, with the added advantage of rapid recovery (2 minutes). Either drug is preferable to no reversal at all because they reduce the duration of blind paralysis.

Sugammadex

A new method of reversing **neuromuscular** blockade might be available in the near future. Sugammadex, previously called *ORG 25969*, leads to restoration of normal **neuromuscular** function not by interfering with acetylcholine, the nicotinic receptor or acetylcholinesterase, but by selectively binding to rocuronium, and to a lesser extent to vecuronium and pancuronium.[152] The compound is a cyclodextrin, made up of eight sugars arranged in a ring to make a center to accommodate the rocuronium molecule. Once bound, rocuronium is held in place by polar side chains attached to the ring. Because sugammadex does not bind to any known receptor, it is devoid of major cardiovascular or other side effects. It does not

bind **neuromuscular blocking** drugs that do not have a steroid nucleus. The benzylisoquinolines, such as atracurium, cisatracurium and mivacurium, and succinylcholine are unaffected by sugammadex.

Mechanism of Action

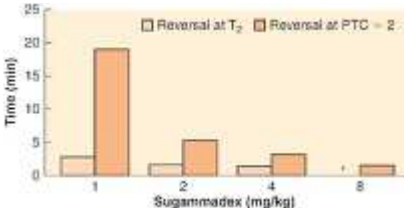
Sugammadex has a molecular weight of 2,178 Daltons[152] and binds with rocuronium in a 1:1 molar ratio. The rocuronium molecule is less bulky (610 Daltons), so 3.6 mg (or mg/kg) of sugammadex is required to bind 1.0 mg (or mg/kg) of rocuronium. Binding is tight, but not irreversible. This means that rocuronium-sugammadex complexes form while some others break up into their two constituents. The dissociation constant has been estimated to be 0.1 μM,[152] and it is not known whether it is affected by pH, temperature, type of fluid or tissue, or other factors. After injection of sugammadex, evidence suggests that binding of rocuronium to sugammadex in plasma leads to a marked decrease in free (unbound) rocuronium concentration,[153] leading to the establishment of a concentration gradient of rocuronium between the **neuromuscular** junction and plasma. This favors movement of rocuronium from **neuromuscular** junction to plasma, producing less **neuromuscular** block. Vecuronium has less affinity for sugammadex than rocuronium does, and pancuronium has less still.

Pharmacology

In patients receiving rocuronium, return of train-of-four ratio to 0.9 is accelerated by sugammadex in a dose-dependent manner. If sugammadex is given on return of the second twitch in the train-of-four, doses of 2 to 4 mg/kg result in the return of train-of-four ratio to 0.9 within approximately 2 minutes.[154] This interval is shorter than after either neostigmine or edrophonium reversal, when given at approximately the same level of recovery. With lower doses (0.5 to 1 mg/kg) recovery time is longer[154] and reparalysis may be observed.[155] Experience with vecuronium is limited, but studies suggest that approximately the same, or perhaps higher, doses of sugammadex are required for the same effect.[154]

Sugammadex is also effective when blockade is deep, but larger doses are required (Fig. 20-21). When a PTC of 2 is present, which for rocuronium occurs 15 to 20 minutes before return of twitch, the required dose is probably 4 to 8 mg/kg.[156]

Sugammadex could also be used in the case of a failed intubation. If rocuronium 0.6 mg/kg was given, sugammadex 8 mg/kg might be effective as early as 3 minutes after rocuronium injection, and if the dose of rocuronium is doubled to 1.2 mg/kg, one might need 16 mg/kg of sugammadex.[157] The availability of sugammadex might make succinylcholine obsolete for intubation.[152]



View Figure

Figure 20-21. Relationship between time to achieve a train-of-four ratio of 0.9 and dose of sugammadex at moderate (spontaneous recovery to T_2 or two visible twitches) or profound (posttetanic count [PTC] of 2). Dose of sugammadex required is greater with profound blockade. *No data available for moderate blockade. (Data from references 153, 154, and 156.)

Pharmacokinetics

Sugammadex has a volume of distribution that is similar to ECF (13 L). Its terminal half-life is approximately 2 hours.[158] Both sugammadex and sugammadex–rocuronium complexes are excreted unchanged via the kidney. No data are available in renal-failure patients. In patients receiving rocuronium, injection of sugammadex increases the total (free plus bound) plasma concentrations of rocuronium, which suggests that it causes sequestration of rocuronium in the plasma by drawing it from peripheral tissues.

Clinical Use

At the time of writing (end of 2007), sugammadex had not been approved for clinical use anywhere in the world. Not all clinical data had been published, so the following comments should be taken with caution. Although administration of doses as high as 40 mg/kg have been reported as safe, it appears prudent to use the lowest effective dose, to keep costs down and because safety of high doses will be established only after use is widespread. Because the effective dose depends on the depth of blockade, monitoring is recommended, if not essential. For reversal of rocuronium blockade when spontaneous recovery has already started (two to four twitches present), sugammadex 2 to 4 mg/kg will produce faster recovery than neostigmine would, without cardiovascular side effects.[154] When recovery is even greater (four apparently equal twitches), 0.5 to 1 mg/kg might be sufficient, but more data are needed on this.

The usefulness of sugammadex might be even greater in cases of deep blockade, when no twitch is seen after train-of-four stimulation. The use of the PTC mode of stimulation will probably be useful in establishing the dose, but if any PTC count is present, it is expected that 4 to 8 mg/kg will be required.[156] The dose will be doubled in cases of deeper blockade (no PTC count) or rescue after failed intubation. It is expected that as confidence in the efficacy of sugammadex in the context of profound blockade builds up, clinicians might have a tendency to give larger doses of rocuronium. This change in practice could yield some benefits. More profound relaxation provides better and faster intubating conditions, better

surgical conditions, and less damage to the laryngeal structures. Faster and more predictable recovery could diminish the incidence of residual paralysis and reduce turn-around time. But these benefits will come at a cost. Of course, it will be more expensive to establish muscle relaxation if the dose of rocuronium is increased, and the cost of reversal will undoubtedly be substantial, especially if large doses are given consistently. In addition, however, all movement will be abolished during surgery, so an important sign of inadequate analgesia and anesthesia will be lost. It is unclear whether awareness can be totally avoided by the use of BIS monitoring, as large doses of **neuromuscular blocking agents** can depress BIS in certain circumstances.[5] Finally, many foreseeable problems regarding sugammadex have not been addressed, such as its use in renal-failure patients, the management of a patient who has recently received sugammadex who needs surgery (for re-exploration for instance), the interaction with steroid-type drugs or naturally occurring molecules, and the potential for bypassing the postanesthesia care unit. Future experience with this new agent will be critical.

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