Review Article

Neuromuscular Blockers - A Review from Historical Perspective to Recent Advances

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Abstract:

The type of neuromuscular blocking agent (NMBA); the type, timing, and dose of their reversal drugs; the means of monitoring NMB; and the site of monitoring are potentially on the verge of a paradigm shift.

The authors believe that selecting the right NMBA, administering concomitant sedation and analgesic therapy, and using appropriate monitoring techniques mitigate risks for anaesthetized patients. Therefore, the authors review the use of NMBAs in the operation theatre (OT) and critical care setting based on their structure, mechanism of action, side effects, and recognized clinical indications. Further, we highlight the available pharmacologic antagonists, and potential complications related to the use of NMBAs in the OT and ICU setting. Lastly, we describe briefly about neuromuscular monitoring in the clinical setting.

Background

Evolution of neuromuscular blocking agents (NMBAs) commenced with d-tubocurarine (1942) inspired by Amazon-Indian poison arrows.[1]

Sir Walter Raleigh, a British explorer, and adventurer described the use of poisoned arrows in modern-day world in his book titled "Discovery of the Large, Rich and Beautiful Empire of Guiana".[2]

Neuromuscular transmission[3]

The region of approximation between a motor neuron and a muscle cell is the neuromuscular junction (Figure 1). The narrow (20-nm) gap is known as the synaptic cleft. Acetylcholine (ACh) molecules diffuse across the synaptic cleft to bind with nicotinic cholinergic receptors on the motor end-plate, which is a specialized portion of the muscle membrane. For normal muscle contraction, activation of about 500,000 receptors is required.

The receptor has five protein subunits, two α subunits, single β, δ, and ε subunits (Figure 2). If both α binding sites are occupied by ACh, a conformational change in the subunits briefly (1ms) opens an ion channel in the core of the receptor.

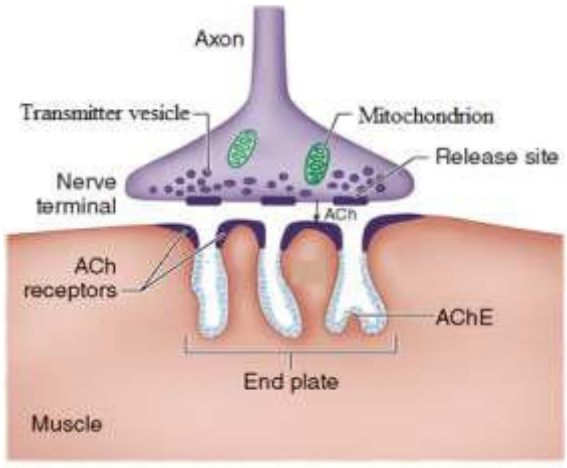


Figure 1: The neuromuscular junction

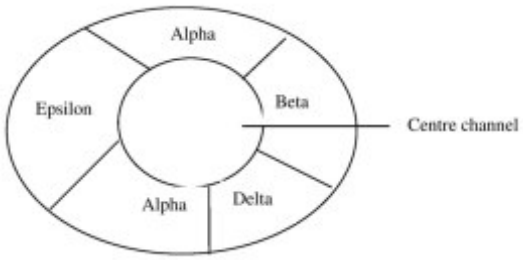


Figure 2: Structure of the ACh receptor

Another iso form, which has γ subunit instead of the ε subunit, is known as fetal or immature receptor. It is also known as extrajunctional as it may be located anywhere in the muscle membrane, inside or outside the neuromuscular junction.

Sodium and calcium flow in and potassium flows out through the open ACh receptor channel. An end-plate potential is thus generated.

ACh is degraded by acetylcholinesterase, which is the true cholinesterase.

Distinctions between depolarizing & nondepolarizing blockade (Table 1)

Depolarizing and nondepolarizing NMBAs have distinct differences in the (1) mechanism of action, (2) response to peripheral nerve stimulation, and (3) reversal of block.

Table 1: Depolarizing and nondepolarizing muscle relaxants

Depolarizing	Nondepolarizing
• Short-acting Succinylcholine	• Short-acting Mivacurium
	• Intermediate-acting Atracurium Cisatracurium Vecuronium Rocuronium
	• Long-acting Doxacurium Pancuronium Pipecuronium

Mechanism of action

Depolarizing muscle relaxants resemble ACh very closely. Therefore, they readily bind to ACh receptors, which generates a muscle action potential. Acetylcholinesterase does not metabolize these drugs unlike ACh. Hence, their concentration does not fall as rapidly in the synaptic cleft. This results in prolonged depolarization of the muscle end-plate.

Opening of the lower gate in peri-junctional sodium channels is time limited. Hence, continuous end-plate depolarization causes muscle relaxation. These sodium channels close after initial excitation & opening and cannot reopen until end-plate repolarization occurs. As long as the depolarizing muscle relaxant continues to bind to ACh receptors, the end-plate cannot repolarize. This is known as phase I block. After a period of time, prolonged end-plate depolarization can cause ionic and conformational changes in the ACh receptor that result in a phase II block, which clinically resembles that of nondepolarizing muscle relaxants.

Nondepolarizing muscle relaxants bind ACh receptors, however they are incapable of inducing conformational change necessary for ion channel opening. No end-plate potential develops because ACh is prevented from binding to its receptors. Even if only one α subunit is blocked, neuromuscular blockade will occur.

Hence, depolarizing muscle relaxants function as ACh receptor agonists, while nondepolarizing muscle relaxants act as competitive antagonists. (A) Those conditions which are associated with a chronic decrease in ACh release, eg, muscle denervation injuries, stimulate a compensatory increase in the number of ACh receptors in the muscle membranes. They also promote expression of immature/extrajunctional isoform of the ACh receptor, which displays low channel conductance properties, along with prolonged open-channel time. There is an exaggerated response to depolarizing muscle relaxants as a result of this up-regulation as more receptors should be depolarized. However, there is a resistance to nondepolarizing muscle relaxants as more receptors should be blocked). (B) Those conditions which are associated with fewer ACh receptors, eg, down-regulation as seen in myasthenia gravis, demonstrate a resistance to depolarizing muscle relaxants and an increased sensitivity to nondepolarizing muscle relaxants.

Response to peripheral nerve stimulation (Table 2 A, B, C)

The following are considered:

- Tetany
- Twitch
- Train-of-four
- Double-burst stimulation (DBS)

Occurance of fade, i.e. gradual diminution of evoked response during prolonged or repeated nerve stimulation, is indicative of a nondepolarizing block

(due to blockade of ACh mobilization). Absence of fade correlates well with adequate clinical recovery. Fade is more obvious during sustained tetanic stimulation or double-burst stimulation.

Posttetanic potentiation refers to the ability of tetanic stimulation during a partial nondepolarizing block to increase the evoked response to a subsequent twitch. This is due to transient increase in ACh mobilization following tetanic stimulation.

A phase I depolarization block, in contrast, does not exhibit fade during tetanus or train-of-four; also it does not demonstrate posttetanic potentiation. When enough depolarizer is administered, however, the quality of the block changes to resemble a nondepolarizing block (phase II block).

Table 2 A: Normal evoked responses]

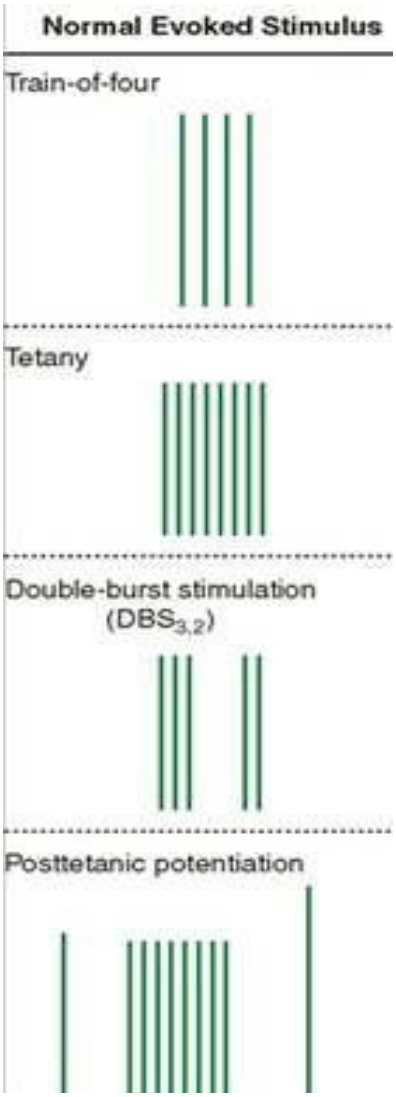


Table 2 B: Evoked responses during depolarizing (phase I and phase II) block

Depolarizing muscle relaxants

Depolarizers first cause muscle contractions (fasciculations) and then paralyse, thus mimicing the effect of acetylcholine at the neuromuscular junction. Succinylcholine (1951) was the first leptocurare used clinically and is the only depolarizer in use.

Succinylcholine

Metabolism & excretion

Succinylcholine has rapid onset of action (30-60 s). It has the advantage of acting within 60 seconds.

It has a short duration of action (typically less than 10 min). Usually, muscle relaxation lasts for under 5 minutes.

The rapid onset of action is largely due to its low lipid solubility (all muscle relaxants are highly charged and water soluble) and the relative overdose that is usually administered.

It is not reversed by anticholinesterases-neostigmine. Plasma cholinesterase causes the effect to wear off quickly. It has a metabolite-succinylmonocholine.

Abnormal metabolism results from:

- Hypothermia
- Low pseudocholinesterase levels
- Genetically aberrant enzyme.

Of the recognized abnormal pseudocholinesterase genes, the dibucaine-resistant (variant) gene, which displays 1/100 of normal affinity for succinylcholine, is the most common. Fluoride-resistant and silent (no activity) are other variants.

Dibucaine number refers to the percentage of inhibition of pseudocholinesterase activity. Dibucaine number is independent of the amount of enzyme, but is proportional to pseudocholinesterase function. Prolonged paralysis from succinylcholine caused by abnormal pseudocholinesterase (atypical cholinesterase) should be treated with continued mechanical ventilation until muscle function returns to normal.

Drug Interactions

A. Cholinesterase inhibitors- Although cholinesterase inhibitors reverse nondepolarizing paralysis, they markedly prolong a depolarizing phase I block by two mechanisms: By inhibiting acetylcholinesterase, they lead to a higher ACh concentration at the nerve terminal, which intensifies depolarization. They also reduce the hydrolysis of succinylcholine by inhibiting pseudocholinesterase.

B. Nondepolarizing relaxants - In general, small doses of nondepolarizing relaxants antagonize a depolarizing phase I block. Because the drugs occupy some ACh receptors, depolarization by succinylcholine is partially prevented. Exception- pancuronium, which augments succinylcholine blockade by inhibiting pseudocholinesterase.

Side effects & clinical considerations

- Hyperkalemia
- Rhabdomyolysis
- Cardiac arrest in children with undiagnosed myopathies

Succinylcholine is contraindicated in the routine management of children and adolescent patients. Now-a-days it is only used in difficult airway and full stomach. The advantage is very rapid onset and short duration.

Unwanted effects include malignant hyperpyrexia, increased intraocular pressure and life-threatening hyperkalaemia. Several deaths attributable to hyperkalaemic cardiac arrest have occurred following its use in children with undiagnosed muscular dystrophies. There is a clinical need for a safer drug that works equally quickly.

Decamethonium is the only other member of the depolarizing NMBA group.[1]

Nondepolarizing muscle relaxants

There is no initial muscle fasciculation, unlike the depolarizing muscle relaxants.

Pancuronium was the first aminosteroidal NMBA introduced in 1964 and its congener vecuronium was introduced in 1984. Both do not release histamine and have a slow onset and unpredictable duration of action in patients with hepatic/renal impairment. However, vecuronium is cardio-stable, unlike pancuronium which causes tachycardia due to its vagolytic action. When Bowman et al[4] demonstrated an inverse relationship between NMBA potency and block onset, quick/rapid onset (within a minute) NMBAs mivacurium (1992), rocuronium (1994), and rapacuronium (1999) were developed. Gantacurium and its congeners comprise the most modern additions.

Important features of some of the nondepolarizers are listed in Table 4.

Table 4: Features of nondepolarizing agents

	Onset/ Duration of action	Ganglion blockade	Histamine release	Cardiac effects	Elimination
Tubocurarine	Slow/ long	Yes +++	Yes +++	Hypotension	Renal
Gallamine	Slow/ long	No	No	Tachycardia	Renal
Pancuronium	Slow/ long	No	No	Tachycardia	Renal/ hepatic
Vecuronium	Slow/ intermediate	No	No	Nil	Hepatic/ renal
Atracurium	Slow/ intermediate	No	Yes +	No	Hofmann
Mivacurium	Slow/ short	No	Yes +	No	Plasma cholinesterase
Rocuronium	Rapid/ intermediate	No	No	No	Hepatic/ renal

Atracurium

Physical Structure

- Contains quaternary group
- A benzylisoquinoline structure is responsible for its unique method of degradation.

Metabolism & excretion

Its pharmacokinetics are independent of renal and hepatic function, less than 10% is excreted unchanged by renal and biliary routes.

A. Ester hydrolysis- This is catalysed by nonspecific esterases, not by acetylcholinesterase or pseudocholinesterase.

B. Hofmann elimination- Spontaneous nonenzymatic chemical breakdown occurs at physiological pH and temperature.

Dosage

- 0.5 mg/kg is administered intravenously over 30-60 s for intubation.
- Available as 10 mg/ml.
- Storage at 2-8 oC
- It loses 5-10% of its potency for each month it is exposed to room temperature.
- At room temperature it should be used within 14 days to preserve potency.
- Side effects & clinical considerations
- Histamine release

A. Hypotension and tachycardia- A slow rate of injection minimizes these effects.

B. Bronchospasm- The drug is avoided in asthmatic patients.

C. Laudanosine toxicity- Laudanosine, the breakdown product of atracurium's Hofmann elimination, has been associated with central nervous system excitation, resulting in elevation of the minimum alveolar concentration and even precipitation of seizures. This occurs with extremely high total dose or hepatic failure.

D. Temperature and pH sensitivity- Action is markedly prolonged by hypothermia, and to a lesser extent by acidosis.

E. Chemical incombatibility- It precipitates as a free acid if introduced into an intravenous line containing an alkaline solution such as thiopental.

F. Allergic reactions-

- Rare anaphylactoid reactions
- IgE-mediated antibody reactions

Cisatracurium

Physical structure

- Stereoisomer of atracurium
- Four times more potent.
- Atracurium contains approximately 15% cisatracurium.

Metabolism & excretion

- Hofmann elimination
- Metabolites are- acrylate, laudanosine
- The amount of laudanosine produced is significantly less than atracurium because of its higher potency.
- Nonspecific esterases do not appear to be involved in the metabolism of cisatracurium.

Dosage

- 0.1-0.15 mg/kg
- Intubating conditions within 2 min
- Infusion rate 1.0-2.0 µg/kg/min.
- The drug is equipotent with vecuronium, and more potent than atracurium.
- It is stored under refrigeration (2-8 oC), and should be used within 21 days after removal from refrigeration and exposure to room temperature.

Side effects & clinical considerations

- Laudanosine toxicity
- pH and temperature sensitivity
- Chemical incompatibility.

Rocuronium

Dosage

The intubating dose is 0.45-0.9 mg/kg, while the maintenance dose is 0.15 mg/kg. The infusion dose for rocuronium is from 5-12 µg/kg/min.

Side effects & clinical considerations

Rocuronium in a dose of 0.9-1.2 mg/kg has an onset of action that approaches succinylcholine (60-90 s), thus making it a suitable alternative for rapid-sequence inductions, however at the cost of a much longer duration of action. The duration of action is comparable to vecuronium and atracurium.

Some clinicians compensate for rocuronium's longer onset of action (compared with that of succinylcholine) by administering it 20 s before propofol or thiopental (the "timing principle"). Disadvantages to this technique include the possibility of delayed administration of induction agent (eg, due to intravenous line precipitate) resulting in a conscious but paralyzed patient.

Gantacurium

Gantacurium belongs to a newer class of non-depolarizing NMBAs: the asymmetric mixed-onium chlorofumarates. Gantacurium is ultra-short acting with rapid onset and a wide safety margin. It is metabolized by chemical degradation, which involves cysteine adduction and pH-sensitive hydrolysis. The onset of action is less than 3 min and could be shortened to approximately 1.5 min by increasing the dose to 4 × ED95. At these doses, the duration of action of gantacurium is approximately 15 min. Transient cardiovascular side effects were observed at doses of 3 × ED95 or higher. Gantacurium is not available in clinical practice at this time.

Reversal of gantacurium-induced neuromuscular block is possible with administration of cysteine.

Advances in reversal of neuromuscular block

Sugammadex[5]

Sugammadex (ORG 25969) is a unique neuromuscular reversal drug; a novel cyclodextrin, the first in a new class of selective relaxant binding agents, which reverse neuromuscular blockade (NMB) with the aminosteroid non-depolarizing muscle relaxants rocuronium and vecuronium. Sugammadex can reverse moderate or deep NMB. The clinical use of sugammadex promises to eliminate many of the shortcomings in current anesthetic practice with regard to antagonism of rocuronium and other aminosteroid muscle relaxants.

Sugammadex is highly agent-specific, however in the future, new broad-spectrum encapsulating agents may become available for all NMBAs.[6]

The cost of sugammadex is significant compared to routine acetylcholinesterase inhibitors. It is unclear whether sugammadex reversal leads to an improved postoperative outcome that justifies its increased cost.

Deep NMB, made possible by sugammadex, may improve surgical working conditions for some procedures and allows for a reduction in insufflation pressures during laparoscopic surgeries.[7-10] However, the impact of deep NMB on patient outcome is still unclear.

L-cysteine[11]

The ultra-short-acting neuromuscular blocker gantacurium is chemically degraded in vitro by rapid adduction of L-cysteine to its central olefinic double bond. Preliminary data have suggested that intravenous L-cysteine abolishes gantacurium blockade. Two new analogues of gantacurium (CW 002 and CW 011) have been synthesized to undergo slower L-cysteine adduction, yielding intermediate duration.

NEUROMUSCULAR MONITORING[12]

Techniques & Complications

A peripheral nerve stimulator gives current with variable frequency & amplitude to a pair of either ECG silver chloride pads or subcutaneous needles. Ulnar nerve stimulation of the adductor pollicis muscle & facial nerve stimulation of the orbicularis oculi is most commonly monitored (Figure 3). 50-mA current across a 1000-Ω load needs to be generated.

Complications

(1) This current is uncomfortable for a conscious patient.

(2) Skin irritation

(3) Abrasion at the site of electrode attachment.

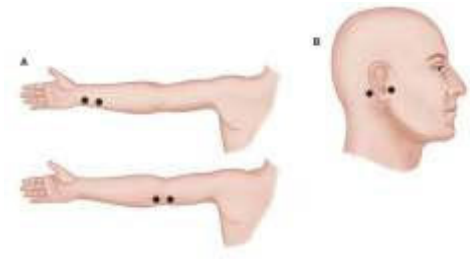


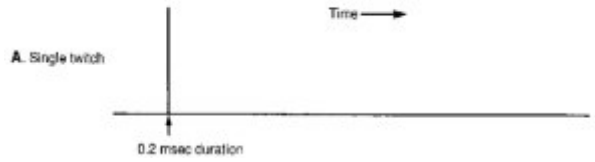
Figure 3 A: Stimulation of the ulnar nerve causes contraction of the adductor pollicis muscle.

B: Stimulation of the facial nerve leads to orbicularis oculi contraction.

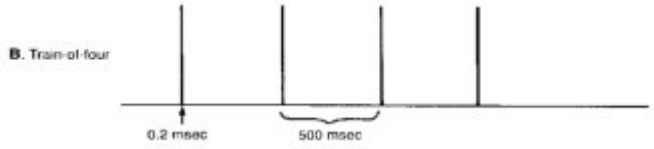
Clinical Considerations

Various patterns of electrical stimulation are shown in Figure 4 A, B, C, D, E, F. The stimulus is 200 μs in duration, square-wave pattern, & equal current intensity.

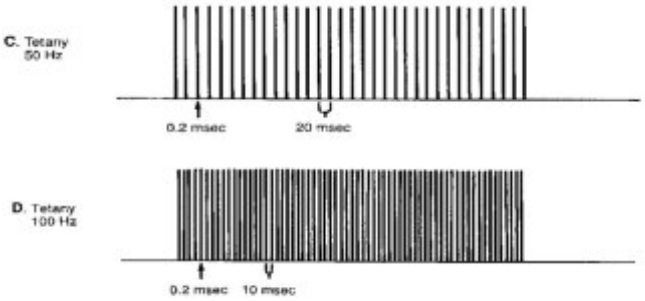
A. Twitch



B. Train-of-four stimulation- This progressively fades as relaxation increases. Disappearance of the fourth twitch represents a 75% block, the third twitch an 80% block, and the second twitch a 90% block. 75-95% block is acceptable.



C. Tetany- Sustained contraction for 5s indicates adequate- but not necessarily complete- reversal from neuromuscular blockade.



D. Double-burst stimulation (DBS)- Less painful to the patient. DBS3,3 pattern and DBS3,2 pattern is followed. DBS is more sensitive than train-of-four stimulation for the clinical evaluation of fade.

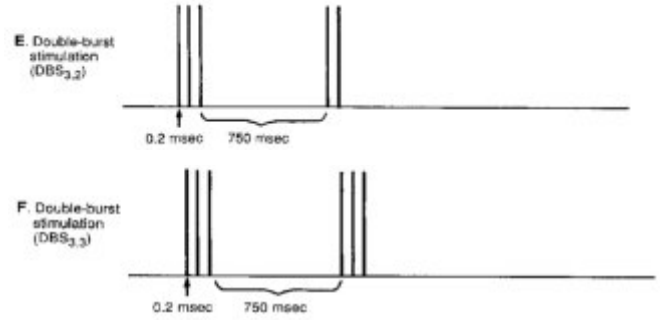


Figure 4 A, B, C, D, E, F: Various patterns of electrical impulses

Different muscles recover at different time intervals from neuromuscular blockade. For example, orbicularis oculis recovers from neuromuscular blockade before the adductor pollicis. Therefore, clinical assessment of the patient should always be done, besides neuromuscular monitoring. Sustained (≥ 5s) head lift, ability to generate an inspiratory pressure of at least -25 cm H2O, & forceful hand grip must be always be taken into account.

Conclusion

Neuromuscular monitoring should be included in the minimum monitoring standards. Gantacurium is a new promising nondepolarizing NMBA with desirable succinylcholine-like onset and duration of action without its side effects. Preliminary data have suggested that intravenous L-cysteine abolishes gantacurium blockade.

This article provides a review for anesthetists to consider modifications in the administration of neuromuscular blockers as per patient requirements.

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