Neuromuscular blocking agents (NMBAs) paralyze skeletal muscles by blocking the transmission of nerve impulses at the myoneural junction. NMBAs have no sedative, amnestic, or analgesic properties and do not prevent muscles from contracting if directly stimulated. These drugs are useful in the intensive care unit (ICU) to improve patient-ventilator synchrony in order to enhance gas exchange and to diminish the risk of barotraumas. They can also be employed to reduce muscle oxygen consumption, facilitate short procedures, prevent unwanted movements in patients with increased intracranial pressure, and facilitate treatment of acute neurologic conditions such as tetanus.

Since introduction of tubocurarine as the 1st neuromuscular blocking agent numerous new drugs for use of muscle relaxation have been developed.

Initially marketed for muscle relaxation to ease endotracheal intubation and provide optimal operating conditions, the application of NMB agents has been expanded to include critically ill patients in ICU and emergency Dept.

Such indications include:

- Early resuscitation (including intubation)
- Refractory hypoxemia e.g. ARDS - will decrease oxygen consumption and optimize chest wall compliance, to allow inverse ratio/prone ventilation
- Decrease pressure on surgical repair sites (i.e., tracheal reconstruction or cardiac repairs)
- Raised intracranial pressure - stops coughing and patients resisting ventilation
- Status epilepticus and tetanus

The ideal NMBA for use in intensive care produces an early, titratable paralysis, has a moderately rapid offset of action (less than 15 minutes) to allow for repeated neurologic assessment, no adverse hemodynamic or other adverse physiologic effects, elimination independent of hepatic or renal function, inactive metabolites, no propensity to accumulate, stability over 24 hours to allow for continuous infusion, and modest cost.

1. Neuromuscular Agents are classified as:
   1. Depolarizing muscle relaxants - Suxamethonium
   2. Non depolarizing muscle relaxants –
      A. Amino steroidal Compounds - Pancuronium, Pipecuronium, Vecuronium, Rocuronium
      B. Benzylisoquinolinium Drugs - Atracurium, Cis-atracurium, Dxacurium

NMBAs with active metabolites include pancuronium, vecuronium, and atracurium. NMBAs that are dependent upon renal clearance (e.g., doxacurium, metocurine, pancuronium, pipecuronium, and tubocurarine) accumulate in patients with renal failure if not properly dose adjusted to PNS response (Table 1).
These agents are classified based upon their structure, mechanism of action, and pharmacokinetic properties.

Structurally, NMBAs have either an amino steroidal or benzylisoquinolinium nucleus. They are classified as either depolarizing or non-depolarizing.

Depolarizing NMBAs physically resemble acetylcholine. Depolarizing agents bind to and activate nicotinic acetylcholine receptors resulting in depolarization of the postsynaptic membrane of striated muscle. Depolarizing NMBAs physically resemble acetylcholine.

Suxamethonium is only agent used for rapid sequence intubation (RSI), it has limited application in the ICU setting due to its short half-life.

Non-depolarizing agents also bind to acetylcholine receptors, but instead of activating them they act as competitive antagonists.

Pharmacokinetic ally, NMBAs differ in their duration of action and route of elimination.

Additionally, differences exist in the degree of histamine release, vagal block, risk of prolonged blockade, and cost of drug administration.

**D-Tubocurarine.** Tubocurarine was the first nondepolarizing NMA to gain acceptance and usage in the ICU.

This long-acting benzylisoquinolinium agent is rarely used in ICUs because it induces histamine release and autonomic ganglionic action. Metabolism and elimination are affected by both renal and hepatic dysfunction.

**ATRACURIUM.**

Atracurium is an intermediate-acting NMA with minimal cardiovascular adverse effects and is associated with histamine release at higher doses. It is inactivated in plasma by ester hydrolysis and Hofmann elimination so that renal or hepatic dysfunction does not affect the duration of blockade.

Atracurium has been administered to various critically ill patient populations, including those with liver failure brain injury or multiple organ dysfunction syndromes (MODS), to facilitate mechanical ventilation. Recovery of normal neuromuscular activity usually occurred within one to two hours after stopping the infusions and was independent of organ function.

Long-term infusions have been associated with the development of tolerance, necessitating significant dose increases or conversion to other NMBAs.

**CISATRACURIUM.**

An isomer of atracurium is an intermediate acting benzylisoquinolinium NMA that is increasingly used in lieu of atracurium. It produces few, if any, cardiovascular effects and has a lesser tendency to produce mast cell degranulation than atracurium. Cisatracurium is also metabolized by ester hydrolysis and Hofmann elimination, so the duration of blockade should not be affected by renal or hepatic dysfunction. Prolonged weakness has been reported following the use of cisatracurium.

**DOXACURIUM.**

Doxacurium, a long-acting benzylisoquinolinium agent, is the most potent NMA currently available.

Doxacurium is essentially free of hemodynamic adverse effects.

**MIVACURIUM.**

Mivacurium is one of the shortest-acting NMBAs currently available. It consists of multiple stereo isomers and has a half-life of approximately two minutes, allowing for rapid reversal.

---

**Table 1: Dosing Guidelines and Pharmacodynamics Parameters of NMB Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug (Trade Name, Manufacturer)</th>
<th>Intubation Dose, mg/kg</th>
<th>Onset, min</th>
<th>Duration, min</th>
<th>Repeat Bolus, mg/kg</th>
<th>Average Infusion Rate, (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-short acting</td>
<td>Succinylcholine (various)</td>
<td>0.6 (0.3-1.1)</td>
<td>1</td>
<td>4-6</td>
<td>0.04-0.07</td>
<td>2.5-4.3 mg/min (0.5-10)</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>Atracurium (various)</td>
<td>0.4-0.5</td>
<td>3-5</td>
<td>20-35</td>
<td>0.08-0.1</td>
<td>5-9 mcg/kg/min (2-15)</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium (Nimbex, GlaxoWellcome)</td>
<td>0.15-0.2</td>
<td>1.5-2</td>
<td>55-61</td>
<td>0.03</td>
<td>1-2 mcg/kg/min (1-3)</td>
</tr>
<tr>
<td></td>
<td>Rocuronium (Zemuron, Organon)</td>
<td>0.6 (0.45-1.2)</td>
<td>1-3</td>
<td>22-67</td>
<td>0.1-0.2</td>
<td>10-12 mcg/kg/min (4-16)</td>
</tr>
<tr>
<td></td>
<td>Vecuronium (various)</td>
<td>0.08-0.1 (up to 0.28)</td>
<td>2.5-3</td>
<td>25-30</td>
<td>0.01-0.015</td>
<td>1 mcg/kg/min (0.8-1.2)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Pancuronium (various)</td>
<td>0.06-0.1</td>
<td>2-4</td>
<td>60-100</td>
<td>0.01-0.06</td>
<td>-</td>
</tr>
</tbody>
</table>

* NMB agents should always be used in combination with sedative and/or anesthetic agents.  †Dosing information pertains only to adults and may vary based on the use of co-induction agents; ‡The onset of time to maximum block or time to good/excellent intubation conditions is dose dependent; §Clinically effective duration of action; † Infusion doses reflect initiation after early evidence of spontaneous recovery from the initial bolus dose. Based on prescribing information/manufacturer’s data and reference 4.
Use of Neuromuscular Blocking Agents in ICU

ADVERSE EFFECTS
Anaphylaxis to NMBAs is rare
The drugs have no known effects outside of muscles and autonomic ganglia. Nevertheless, NMBAs have the potential for severe adverse effects such as hypotension and prolonged paralysis.

Cardiovascular effects — Adverse cardiovascular side effects associated with NMBAs are related to stimulation or blockade of the autonomic nervous system and vasodilatation due to histamine release. The drugs with the lowest risk of cardiovascular complications are cisatracurium, doxacurium, pipercuronium, rocuronium, and vecuronium

Prolonged paralysis — prolonged paralysis following drug discontinuation results from accumulation of drug and/or active metabolites, or an acute myopathy

There are probably two adverse events related to prolonged paralysis following discontinuation of NMBAs.

It is defined the first, “prolonged recovery from NMBAs,” as an increase (after cessation of NMBA therapy) in the time to recovery of 50–100% longer than predicted by pharmacologic parameters. This is primarily due to the accumulation of NMBAs or metabolites.

Prolonged paralysis following drug discontinuation may result from an NMBA-associated syndrome of acute myopathy with selective loss of myosin filaments. Most reported cases have occurred after combined treatment with corticosteroids and NMBAs, suggesting that myopathy is the result of an interaction between the two drugs. However, acute myopathy also has been described after prolonged treatment with an NMBA or a corticosteroid alone

By comparison, the second, AQMS, presents with a clinical triad of acute paresis, myonecrosis with increased creatine phosphokinase (CPK) concentration, and abnormal electromyography (EMG). The latter is characterized by severely reduced compound motor action potential (CMAP) amplitudes and evidence of acute denervation. In the beginning, these syndromes are characterized by neuronal dysfunction; later (days or weeks), muscle atrophy and necrosis may develop.

Enhanced paralysis from other common ICU problems such as hypokalemia, aminoglycoside antibiotics, hypophosphataemia, hypermagnesemia, metabolic acidosis, hepatic or renal failure

RECOMMENDATIONS
Patients MUST be mechanically ventilated prior to administration of NMBAs.

Adequate sedative and analgesic therapy MUST be provided prior to and for the duration of neuromuscular blockade.

Cisatracurium-based NMBA therapy should be monitored using either clinical

Assessment of respiratory function or peripheral nerve stimulation [Train of Four (TOF) monitoring].

For patients for whom vagolysis is contraindicated (e.g., those with cardiovascular disease), NMBAs other than pancuronium may be used

Accumulation especially with amino steroids in ARF

Because of their unique metabolism, cisatracurium or atracurium is recommended

For patients with significant hepatic or renal disease

Prolonged paralysis after discontinuation of NMBA occurs due to accumulation and results in severe myopathy critical illness polyneuropathy occasionally (esp. if steroids used as well)

Cisatracurium is NMBA of choice.

In patients who is able to tolerate interruption of neuromuscular blockade, the NMBA

Infusion should be interrupted daily to assess motor function and level of sedation.

Physical therapy should be provided to patients on NMBAs.

They cannot be left unsupervised because interruption of the ventilator circuit can be fatal

Since all NMBAs inhibit the cough reflex, suctioning of the endotracheal tube to remove accumulated secretions should be performed as needed.

Artificial tears should be instilled every two to four hours and eyelids should be taped shut to prevent corneal drying and ulceration

Patients require frequent turning and dry, wrinkle-free bedding in order to prevent skin breakdown and decubitus ulcers

Prophylactic deep venous thrombosis therapy with either low dose subcutaneous heparin or mechanical compression devices is required

The head of the bed should be elevated to reduce the risk of aspiration, particularly during enteral feeding.

Pupillary reflexes should be closely monitored to assess neurologic status (but are unreliable if pancuronium is used because of its antimuscarinic effects).

Discontinuation — Tapering the dose is not necessary when neuromuscular blockade is discontinued. Sedation and
analgesia adequate for patient comfort must be maintained as the NMBA is discontinued.

The action of nondepolarizing NMBAs can be reversed by administration of an anticholinesterase drug such as neostigmine, 0.035-0.07 mg/kg

Remember what your goal is: to keep the patient in synch with the vent, and to improve CO2 clearance. If you meet those goals, there you are. If you can get there without paralyzing your patient, so much the better

Sensitivity to NMBAs varies and the metabolism of NMBAs cannot always be predicted in the critically ill. Therefore, we recommend monitoring the degree of neuromuscular blockade

Monitoring Neuromuscular Blockade is done by

Monitoring should ideally be performed using a nerve stimulator (e.g. train-of-four count).

Clinical monitoring such as cardiovascular reflexes to noxious stimuli should also be observed.

Skeletal muscle movement and respiratory effort forms the foundation of clinical assessment

TOF monitoring of PNS remains the easiest and most reliable method available despite its shortcomings and technical pitfalls

Train-of-four is the more commonly used method and involves electrical stimulation of a peripheral motor nerve with four sequential stimuli over a two second period and observation of the responses of a muscle innervated by the stimulated nerve

The stimulator delivers a series of four electrical signals, (called a “train-of-four” – there’s a button that says “TOF” on the box), to a specific site over the ulnar nerve. You hold the patient’s hand as though shaking hands, with your thumb hooked in theirs. If the patient is not paralyzed at all, each of the four signals in the TOF will generate a “twitch” response in the patient’s thumb – you’ll feel it pull against yours: 1,2,3,4. If the patient is fully paralyzed, you won’t feel any twitch response at all. Try the twitch with the output dial on the box at different settings – the knob can be set from 1-10.

The goal is a response of one or two twitches out of a train of four – meaning, you feel the patient’s thumb twitch under yours once, or twice, in response to the first, or first two signals in the train. The study reveals this level of paralysis means that your patient will be “paralyzed enough”, but will not be so saturated with the drug that it takes too long to wear off.

The depth of blockade should be assessed with PNS every 2 to 3 hours until the NMBA dose is stable, then every 8 to 12 hours.32 If no or one twitch is present, the dose should be reduced by 10 percent; if three or four twitches are present, the dose should be increased by 10 percent

With the monitoring with PNS requires significantly less drug and recovered neuromuscular function and spontaneous ventilation approximately 55 percent faster than the control group; patients with renal insufficiency appeared to derive the most benefit for PNS-guided therapy

There is inadequate data to support the routine use of NMBAs.

Patients receiving NMBAs require meticulous care because the potential for complications is great. All paralyzed patients require the special precautions:

Neuromuscular blocking agents (NMBAs) should be considered an intervention of last resort due to the multiple complications associated with their use.