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Neuromuscular Blocking Agents (NMBAs): An Overview

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Abstract

Neuromuscular blocking agents (NMBAs) are commonly used to paralyze skeletal muscles during surgery conducted under general anesthesia and for patients requiring in tubation for airway management. These medications are used in emergency departments, intensive care units, interventional radiology areas, and even medical and surgical units. NMBAs render patients unable to move or breathe and are considered high-alert drugs because misuse can lead to catastrophic injuries or death, especially when administered to patients who are not properly ventilated. Between June 2004 and March 2009, Pennsylvania healthcare facilities submitted 154 event reports that mentioned medication errors involving the use of NMBAs. Analysis reveals that the most common medication error event types associated with this class of medications were wrong-drug errors (37%)followed by wrong-dose/over dosage errors (16.2%).Further analysis showed that 47.4% of the intended medications were not NMBAs, including cases in which the patient was harmed. Strategies to address these problems include limiting access to NMBAs, segregating NMBAs from other medications, sequestering and affixing warning labels to vials of NMBAs stocked in the pharmacy, and requiring independent double-checks before dispensing and administering NMBAs.

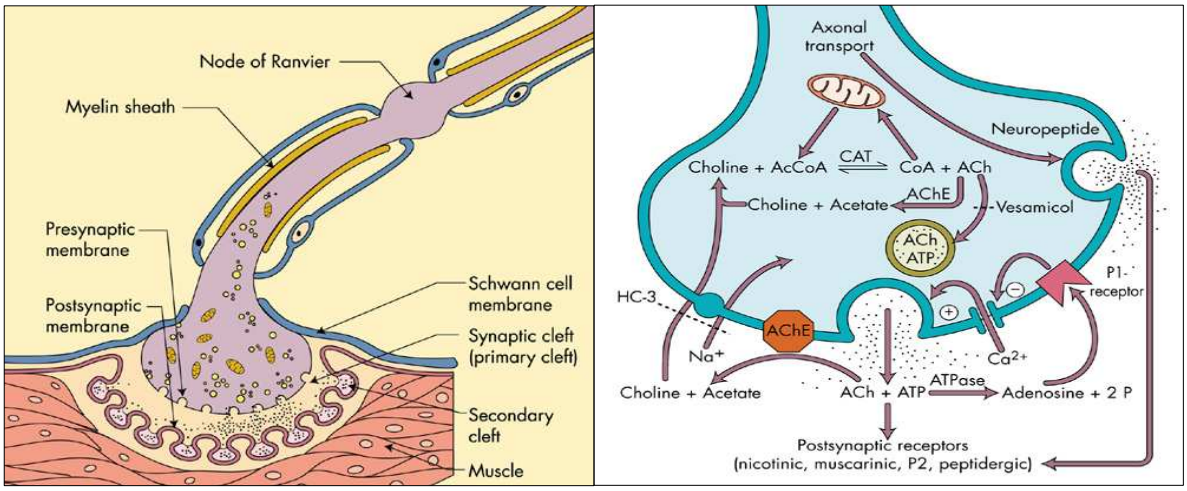
Keywords: NMBAs, (NMJ), Non-depolarizing blocking agents, Depolarizing blocking agents, Tubocurarine.

Introduction

A neuromuscular junction (NMJ) is the synapse or junction of the axon terminal of a motoneuron with the motor end plate, the highly-excitable region of muscle fiber plasma membrane

responsible for initiation of action potentials across the muscle's surface, ultimately causing the muscle to contract. In vertebrates, the signal passes through the neuromuscular junction via the neurotransmitter acetylcholine. Motor neuron (efferent) axons originating in the spinal cord enter muscle fibers, where they split into many unmyelinated branches. These terminal fibers run along the myocytes to end at the neuromuscular junction, which occupies a depression in the sarcolemma. Each motor neuron can innervate from one to over 25,000 muscle fibers, but muscle fiber receives inputs from only one motor neuron. On the muscle side of the junction, the muscle fiber is folded into grooves called prejunctional folds that mirror the presynaptic active zones, the spaces between the folds contain the enzyme acetylcholinesterase.[1]

During development, the growing end of motor neuron axons secrete a protein known as agrin.This protein binds to several receptors on the surface of skeletal muscle. The receptor which seems to be required for formation of the neuromuscular junction is called "LRP4" and not the formerly considered MuSK protein (Muscle specific kinase). MuSK is a receptor tyrosine kinase - meaning that it induces cellular signaling by causing the release of phosphate molecules to particular tyrosines on itself, and on proteins which bind the cytoplasmic domain of the receptor Upon activation by its ligand agrin, MuSK signals via two proteins called "Dok-7" and "rapsyn", to induce "clustering" of acetylcholine receptors (AChR). In addition to the AChR and MuSK, other proteins are then gathered, to form the endplate to the neu- romuscular junction. The nerve terminates onto the endplate, forming the NMJ.[2]



Figures 1&2- Showing nerve terminal on the end plate, forming NMJ & neurotransmission of Ach on NJM

History

It is one of the chemicals that can be obtained from curare, itself an extract of *Chondrodendron tomentosum*, a plant found in South American jungles which is used as a source of arrow poison. Native Indians hunting animals with this poison were able to eat the animal's contaminated flesh without being affected by the toxin because tubocurarine cannot easily cross mucous membranes and is thus inactive orally. Medically, first used in 1912. Introduced in anesthesia in 1942. The correct chemical structure was only elucidated circa 1970, even though the plant had been known since the Spanish Conquest. The word *curare* comes from the South American Indian name for

the arrow poison: "ourare". Presumably the initial syllable was pronounced with a heavy glottal stroke. Tubocurarine is so called because the plant samples containing it were first shipped to Europe in tubes. Today, tubocurarine has fallen into disuse in western medicine, as safer synthetic alternatives such as atracurium are available. However, tubocurarine is still used in the United States and elsewhere as part of the lethal injection procedure.[3]

Curare was used for centuries by South American Indians to hunt game, and its evolution into the designer drugs of today began when tales of the mysterious ‘flying death’ were brought home to the Old World by Spanish conquistadors. Peter Martyr d'Anghera, a chronicler in the Court of King Ferdinand and Queen Isabella, first wrote of the poisoned arrows in his book De Orbe Novo, a collection of letters written in 1516 this was a blend of fact and fantasy that contributed to the mystique of curare and drew many men in its quest, some to their deaths. In 1594, Sir Walter Raleigh visited Venezuela, and his book Discovery of the Large, Rich and Beautiful Empire of Guiana mentions the poisoned arrows. One of his lieutenants called the poison ‘ourari’. Ourari is possibly a corruption of the Indian word urinary from uria, meaning bird and eor to kill European attempts at rendering the Indian word led to several versions including ourara, urali, urare, woorari, wourali and curare Wars between the English, the Spanish and the Portuguese prevented further exploration till the 18th century. Edward Bancroft, a physician, spent five years in South America and brought back samples of crude curare. Using these samples, Sir Benjamin Brodie demonstrated that small animals could be kept alive after being injected with curare by inflating their lungs with bellows. In 1804 Charles Waterton, an eccentric explorer, left the family seat Walton Hall in Yorkshire to manage the sugar estates owned by his family in Demerara, South America. He obtained several samples of wourali from a native tribe and tried it out on large animals. In 1814, he demonstrated to an audience that included Sir Benjamin Brodie the effects of wourali on three asses. The first ass was injected with wourali in the shoulder and died. The second had a tourniquet tied around its foreleg and wourali was injected below the tourniquet; the ass was alive and active as long as the tourniquet was in place but died soon after the tourniquet was removed. The third ass appeared to die after having wourali injected but was resuscitated by means of bellows and lived on in peace as Wouralia, for her travails in the cause of science she earned an obituary in the St James Chronicle, a local newspaper.

Claude Bernard published the details of his experiments on frogs in 1846. He showed that curare injected into a limb prevented the muscle contraction in response to nerve stimulation; the muscle continued to respond when stimulated directly. Curare when applied directly to the nerve failed to abolish muscle contraction in response to either nerve stimulation or direct muscle stimulation—proof that curare acted at the nerve-muscle junction. In the 1860s the Edinburgh scientists Thomas Richard Fraser and Alexander Crum Brown, working on the relation between chemical structure and biological activity, discovered that when alkaloids such as atropine, brucine, codeine, morphine and nicotine had their nitrogen atoms changed from the tertiary to the quaternary form, they acquired curare-like activity. This was the precursor to much of the work on neuromuscular blocking drugs that took place after the Second World War.

The turn of the century heralded several momentous developments. In Great Britain, Sir Henry Dale and colleagues working at the National Institute of Medical Research established the role of acetylcholine and the chemical basis of neuromuscular transmission. Harold King isolated d-

tubocurarine from a museum sample of curare. He established that it was a bulky rigid molecule with two quaternary ammonium groups at either end.Richard Gill, an American living in Ecuador, developed multiple sclerosis and returned to the United States in search of a cure. His neurologist Walter Freeman suggested that he might benefit from curare. Gill returned to the jungles of Ecuador and brought back twenty-five pounds of crude curare and several botanical samples. These samples were identified as plants of two families—Menispermaceae, which include the genus Chondrodendron; and Loganiaceae, which include the genus Strychnos. Gill offered the curare to E R Squibb and Sons with the hope that their researchers would come up with a drug effective in multiple sclerosis.

Table 1- Development of neuromuscular blockers

Discovering year of Drug	Name of discovering drug
1942	Curare
1947	Gallamine
1949	d-Tubocurarine
1951	SCh
1960	Pancuronium
1964	Alcuronium
1970	Fazadinium
1980	Atracurium
1992	Mivacurium
1994	Rocuronium
1995	Cis-atracurium
2000	Rapacuronium

The crude curare was investigated in their laboratories. Oscar Winter Steiner and James Dutcher in 1942 were the first to isolate the alkaloid d-tubocurarine from biologically authenticated samples of Chondrodendron tomentosum. A H Holladay of Squibb devised his rabbit 'head-drop' bioassay and standardized the commercial preparation of curare as Intocostrin.A E Bennett, a neuropsychiatrist who was on the verge of abandoning convulsive shock therapy because of the high incidence of spinal fractures, decided to try and modify the convulsion with curare. In June 1940, Bennett presented a film on the use of curare at the 91st annual session of the American Medical Association. Lewis Wright of Squibb saw this film and, thinking the drug might be of use to anesthetists, donated some Intocostrin to E A Rovenstine of New York University to experiment with. Rovenstine passed it on to one of his residents, E M Papper, who tried it on two patients receiving ether anaesthesia. Both of them became apnoeic and had to be ventilated manually all through the night. Endotracheal intubation was uncommon in those days.

Harold Randall Griffith, an anaesthetist at the Homeopathic Hospital in Montreal, was an ardent enthusiast for cyclopropane, and realized that the occasional episodes of apnoea induced by this agent could be overcome by mastering the skill of endotracheal intubation. He was confident of his ability to circumvent the major problem with the use of curare, and on 23 January 1942 he and his resident Enid Johnson administered curare to a young man undergoing appendicectomy.

Table-2 Pharmacological comparison of neuromuscular blocking agents

Agent	Times to onset (Sec.)	**Duration** (min.)	**Side-effects**	**Clinical use**	Storage
Mivacurium (Mivacron)	90	12-18	hypotension (transiently), by release of histamine	No longer manufactured secondary to marketing, manufacturing, financial concerns	Refrigerated
Atracurium (Tracrium)	90	30 min or less	hypotension, renal failure	Widely	Refrigerated
Doxacurium (Nuromax)		long	hypotension, renal failure		
Cisatracurium (Nimbex)	90	60-80	does not cause release of histamine		Refrigerated
Vecuronium (Norcuron)	60	30-40	Prolonged paralysis and promote muscarinic block	Widely	non-refrigerated
Rocuronium (Zemuron)	75	45-70	promote muscarinic block		non-refrigerated
Pancuronium (Pavulon)	90	180 or more	tachycardia	Widely	non-refrigerated
Tubocurarine (Jexin)	300 or more	60 - 120	hypotension	Rarely	
gallamine (Flaxedil)	300 or more	60 - 120[1]	tachycardia		
Pipecuronium	90	180 or more	tachycardia		Non-refrigerated

The credit for introducing curare to anaesthetics belongs to him. Griffith and Johnson reported their use of curare in July 1942, and the introduction to their report is memorable: ‘Every anaesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anaesthesia. A commemorative stamp issued by Canada in 1991 honours Griffith's contribution to anaesthesia.The Second World War brought a halt to work on curare-like drugs at the UK National Institute of Medical Research, but American doctors stationed in England brought word of the use of curare as a muscle relaxant. John Halton, an anaesthetist from Liverpool, persuaded an American friend from the bomber squadron stationed at Burtonwood to bring back Intocostrin from the United States. He and Cecil Gray used the drug on patients and were highly gratified by the results they obtained. Their experiences with curare were reported in 1946 and laid the basis of what became known as the Liverpool technique—a triad of narcosis, analgesia and muscle relaxation that in essence remains in use today[4].

Classification of neuromuscular blocking agents
These drugs fall into two groups:

Non-depolarizing blocking agents: These agents constitute the majority of the clinically-relevant neuromuscular blockers. They act by blocking the binding of ACh to its receptors, and in some cases, they also directly block the ionotropic activity of the ACh receptors. Below are some of the more common agents that act as competitive antagonists against acetylcholine at the site of postsynaptic acetylcholine receptors.Tubocurarine, found in curare of the South American plant genus *Strychnos*, is the prototypical non-depolarizing neuromuscular blocker. It has a slow onset (>5 min) and a long duration of action (1–2 hours). Side effects include hypotension, which is partially explained by its effect of increasing histamine release, a vasodilator, as well as its effect of blocking autonomic ganglia It is excreted in the urine. This drug needs to block about 70-80% of the Ach receptors for neuromuscular conduction to fail, and hence, for effective blockade to occur. At this stage, end-plate potentials (EPPs) can still be detected, but are too small the reach the threshold potential needed for activation of muscle fiber contraction[5].

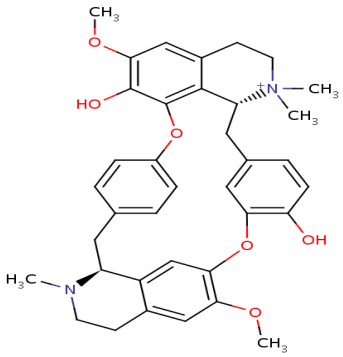
Depolarizing blocking agents- These agents act by depolarizing the plasma membrane of the skeletal muscle fiber. This persistent depolarization makes the muscle fiber resistant to further stimulation by ACh. Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to acetylcholine. However, these agents are more resistant to degradation by acetyl cholinesterase, the enzyme responsible for degrading acetylcholine, and can thus more persistently depolarize the muscle fibers. This differs from acetylcholine, which is rapidly degraded and only transiently depolarizes the muscle. There are two phases to the depolarizing block. During phase I (*depolarizing phase*), they cause muscular fasciculation's (muscle twitches) while they are depolarizing the muscle fibers. Eventually, after sufficient depolarization has occurred, phase II (*desensitizing phase*) sets in and the muscle is no longer responsive to acetylcholine released by the motoneurons. At this point, full neuromuscular block has been achieved. The prototypical depolarizing blocking drug is succinylcholine (suxamethonium). It is the only such drug used clinically. It has a rapid onset (30 seconds) but very short duration of action (5–10 minutes) because of hydrolysis by various cholinesterases (such as butyrylcholinesterase in the blood). Succinylcholine was originally known as diacetylcholine because structurally it is composed of two acetylcholine molecules joined with a methyl group. Decamethonium is sometimes, but rarely, used in clinical practice. Inhibition of acetyl cholinesterase may be used to cause the same effect as a depolarizing neuromuscular block.

Table 3- Pharmacokinetics effect of neuromuscular blocking agents

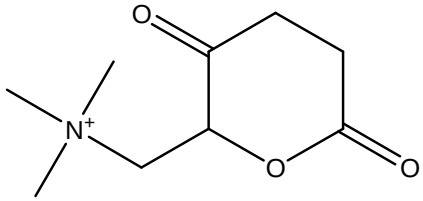
Drug	Metabolism	Renal	Biliary
Succinylcholine	98 - 99 %	< 2 %	--
Mivacurium	95 – 99 %	< 5 %	--
Atracurium	70 – 90 %	10 – 30 %	Laudanosin
Cis-atracurium	70 – 90 %	10 – 30 %	Laudanosin
Vecuronium	30 – 40 % (Hepatic)	40 % (metabolites)	10 – 20 % (metabolites)
Pancuronium	10 – 20 % (Hepatic)	60 – 80 %	10 %
Rocuronium	Minimal (Hepatic)	30 – 40 %	60 %

A prototype of drugs used in neuromuscular blocking agents

Tubocurarine- *Tubocurarine* chloride is an alkaloid of the benzylisoquinoline type. It is an antagonist of nicotinic neuromuscular acetylcholine receptors that is used to paralyse patients undergoing anaesthesia. d-tubocurarine and that it produced a transient augmentation of contraction. The Paton group commented on the fasciculation that preceded the onset of block and speculated as to its cause: C10 produces neuromuscular block by initiating some active response in the endplate or muscle fibre. They also showed that, unlike d-tubocurare, decamethonium was not reversed by anticholinesterase agents.[7]

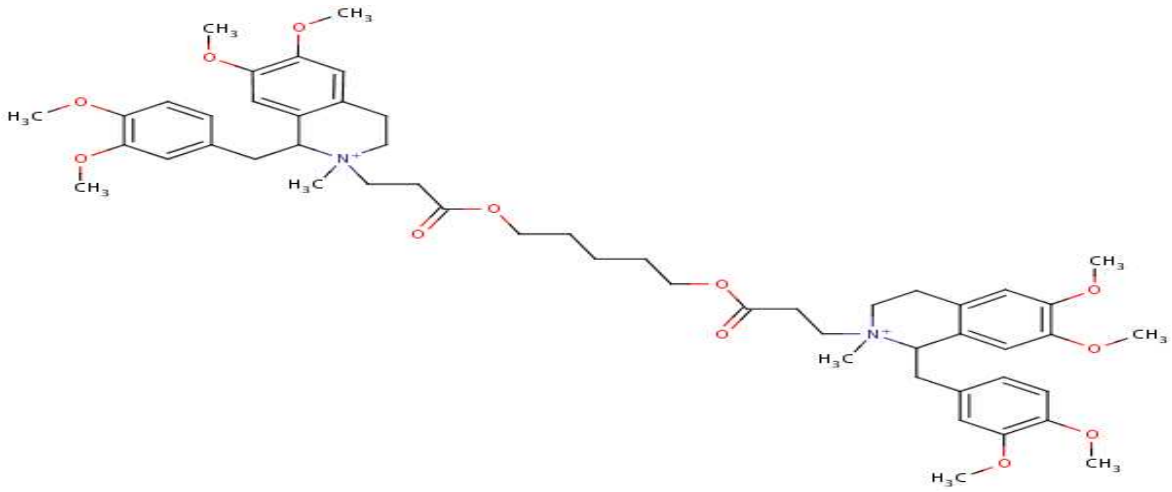


Succinylcholine-Depolarizing neuromuscular blockers like succinylcholine (SCh) act by binding with the receptors to which acetylcholine normally binds. However, SCh binds with the receptors for a much longer period of time as compared to acetylcholine, thereby causing persistent depolarization of the muscle end plate. This results in blockage of sequences which lead. The only depolarizing NMBA currently used. Memb. Potential returns to resting state despite presence of the drug and the transmission is blocked. Dose of succinylcholine is 1 mg / kg, block lasts 8 min.[8]

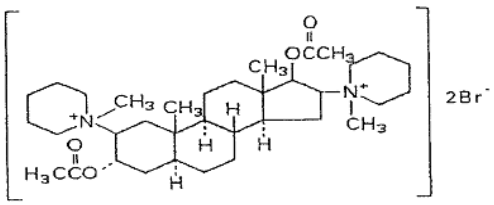


Atracurium- Atracurium besylate, 2,2'-(3,11-dioxo-4,10-dioxatridecylene)-bis-[6,7-dimethoxy-1-(3,4-dimethoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium] dibenzenesulphonatc, is one of a new series of competitive neuromuscular blocking agents. An i.v. dose of 0.25 mg kg^{-1} produced complete paralysis in anaesthetized cats, dogs and rhesus monkeys; paralysis was of medium duration and was readily antagonized by neostigmine. Vagal blockade occurred only after doses 8–16 times greater than the full neuromuscular paralysing dose and effects on sympathetic mechanisms were minimal. Hypotension and bradycardia were evident after supramaximal doses of 4 mg kg^{-1}i.v. and these effects, together with circulatory depression, were probably attributable to histamine release. *In vitro* studies have shown that the non-enzymic decomposition of atracurium by "Hofmann Elimination" was enhanced by increasing pH. *In vivo* neuromuscular paralysis was significantly reduced when the arterial pH was increased. There were indications that neither the liver nor the kidney plays a major role in the metabolism and

elimination of unchanged drug. These results are of sufficient interest to merit the evaluation of atracurium in anaesthetized man.[9]



Pancuronium- Pancuronium bromide (Pavulon NA97, Organon) has been shown to be a potent neuromuscular blocking agent (muscle relaxant) with a medium duration of action. It is of non-depolarising type and is readily reversed by neostigmine when required. It is strikingly free from side-effects such as histamine release, ganglion blockade, atropine-like activity or hypotension, and its acute toxicity is extremely low provided adequate ventilation is maintained. The hypotensive effect of halothane is counteracted to some extent by pancuronium, whose neuromuscular blocking action is in fact potentiated not only by halothane but also by ether and thiopentone. Evidence at present suggests that pancuronium is partly excreted unchanged in the urine, but tritiated material has also been demonstrated in the liver.[10]



Recent advanced search in neuromuscular blocking agents

- **ORG 9487**- Amino steroid Low potency, ED 90 = 1.15 mg/kg Rapid onset (similar to SCh @ add.pollicis but vocal cords are resistant) Duration longer than SCh.
- **BW 785 U**- Benzylisoquinolin, onset 60 – 90 sec, duration 10 – 15 min Histamine release → hypotension.
- **Gantacurium (GW 280430 A)** - By GSK, similar to Mivacurium. ED 95 = 0.18 mg/kg3 x ED 95 (0.54 mg/kg): Onset 1.2 - 1.8 min & duration of 15 min Higher doses cause histamine release without change in onset time. Alkaline hydrolysis in plasma + spontaneous formation of cysteine adducts Very little genetic variability.
- **51W89**- One of 10 isomers of Atracurium, Onset & duration like Atracurium. Minimum CV effects, Hofmann elimination" Nearly ideal" relaxant with intermediate duration.

Two previous patents (US Patents 6,177,445 and 6,187,789B1) describe compounds invented in part by Dr. John Savarese, chair of the Weill Cornell Medical College Department of Anesthesiology. These compounds were designed as ultra-short acting nondepolarizing neuromuscular blockers (duration of action 4 to 9 min. in monkeys). The present discovery describes neuromuscular blocking agents which are symmetrical or asymmetrical benzylisoquinolinium or phenylisoquinolinium diesters of fumaric acid. The duration of action in monkeys is exactly within the intermediate-duration range (20-45 minutes), and the cardiovascular effects of these compounds are minimal, even at very high dosage in the range 20 to 100x fully paralyzing doses. The neuromuscular blockade is readily antagonized during established recovery, in conventional fashion, by typical doses of neostigmine 0.05 to 0.08 mg/kg given together with atropine. The latter is given to control the well-known muscarinic side effects of the anticholinesterase. The rapid and complete reversal by cysteine/glutathione of the paralyzing effects of all doses, even huge overdoses, of the new neuromuscular blocking drugs described in this invention, at any stage of neuromuscular blockade, even immediately after the injection of fully paralyzing doses, is a unique property possessed only by the new drugs described in this invention. This is a particularly relevant and important safety issue to clinical practice because, by administering cysteine/glutathione, patients can be safely and quickly restored to normal neuromuscular function at any time during paralysis, even immediately after complete paralysis has been induced, e.g. by a large dose of one of the compounds described in this invention[11-16].

Future possibilities NMBAs

- Incorporation of reversing molecule.
- Reversal by complex formation (Poly anions).
- Reversal by enzymatic hydrolysis[17].

Conclusion

Medical errors involving NMBAs continue to result in patient morbidity and mortality. Increased awareness and action on the part of all parties involved—manufacturers and suppliers, purchasers, and all practitioners involved in the entire medication-use process—are needed to improve the safety of this class of medications. NMBAs should not be administered in the critical care setting (for reasons other than placement of an endotrachealtube) without concurrently medicating the patient for pain or anxiety, despite the lack of obvious symptoms or signs. Neuromuscular blockade is one of the essentials of modern day anesthesia practice. May it be the intubations or intra-operative relaxation, not only that it is beneficial for the attending anesthesiologist but it also facilitates the surgeon. With the advancement of anesthesia practice, it is impossible to think about abdominal, cardiac, head and neck surgeries etc. being undertaken without proper muscle relaxation .Neuromuscular blocking drugs have certainly revolutionized the current anesthesia care but this advancement is also associated with certain risks. To Paralyze a patient and then to reverse it, is certainly a big ask.

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