Script for:
Neuromuscular Blocking Agents
Surgery 101 Podcast
Department of Surgery
University of Alberta

By

Urooj Siddiqui Med 4
University of Alberta

Hello, and welcome to this episode of the UofA Anesthesia Podcast on neuromuscular blocking agents. My name is Urooj Siddiqui; I am a 4th year medical student here at the UofA and also a proud developer of this initiative. The Departments of Surgery and Anesthesiology and Pain Medicine here at the University of Alberta are proud to offer a unique means of educating medical students about the specialty of Anesthesia! I'd also like to recognize and thank Dr. Michael Murphy for his assistance and feedback on this episode.

The objectives of today's podcast are as follows:

- Pharmacology and physiology of muscle relaxants
- Classes of neuromuscular blocking agents
- Importance of neuromuscular blockade in practice
- Monitoring muscle relaxationIndications and contraindications
- Complications

Can you imagine being fully awake yet totally paralyzed, unable to blink an eye, scratch your nose, move your arms and legs or even breathe? That'd be scary, and yet that's exactly what neuromuscular blocking drugs do.

Neuromuscular blocking agents render someone paralyzed so that they cannot move at all. Unbelievable as it may be, these types of paralytic agents are nothing new. They have been around since the primitive ages and were often an integral part of primitive cultures. It all began with South American arrow tip poison which attracted the attention of the European medical community in the early 16th century.

Charles Waterton, an Englishman, took specimens of arrow poison to England from British Guiana in 1812. With Sir Benjamin Brodie and Francis Sibson, Waterton determined that a donkey could survive the poison, if artificial respiration was provided. It wasn't until 1857 that Claude Bernard localized the effects of the drug, now known as curare, to the neuromuscular junction. Surprisingly, even after its effect was localized, the curare poison had no medical indication for nearly 200 years. It wasn't until tracheal intubation and controlled ventilation became popular in the 20th century that the use of curare poison during anesthesia sparked interest.

Obtaining large enough quantities of the curare poison for clinical use is attributed to the combined efforts of husband and wife Richard and Ruth Gill who had lived in Ecuador and knew the native customs with arrow poison. Gill's neurologist, Walter Freeman, suggested that his neurologic syndrome defined by intermittent spasticity might

be relieved if they had enough curare poison for clinical testing. In 1935 Ruth and Richard Gill set off on a 7-month expedition into the jungle, from which they returned with 25 pounds of curare paste. The samples eventually made their way to psychiatrist Abram E. Bennett in Omaha Nebraska, a friend of Walter Freeman's. Bennet began using the drug and eventually learned it could be used to prevent muscle contractions.

Lewis H. Wright was an anesthesiologist at the time. He sought out other anesthetists to try the drug form of curare, called Intocostrin, for skeletal muscle relaxation during surgery. Though initially unsuccessful, Harold R. Griffith and Enid Johnson at McGill University reported the successful use of Intocostrin to relax abdominal skeletal muscles during anesthesia in 1942. The value of Intocostrin was quickly realized, and with the growing popularity of tracheal intubation and positive pressure ventilation, the safe use of skeletal muscle paralysis during anesthesia flourished.

So, despite the seemingly scary nature of neuromuscular blockade agents, their utility is undeniable. The concomitant advent of other anesthetic techniques, such as assisted respiration, have allowed neuromuscular blocking agents to play a vital role in effectively paralyzing patients during surgery to enhance surgical working conditions and outcome.

Physiology & Pharmacology

To understand how neuromuscular blocking agent's work, we must first appreciate the events that occur at the neuromuscular junction, which eventually lead to muscle contraction. The neuromuscular junction is the space between a motor neuron called the synaptic cleft. Depolarization of the motor neuron results in release of vesicles containing acetylcholine (Ach) into the synaptic cleft. The Ach diffuses across the cleft and binds to Ach nicotinic receptors on the muscle cell at the motor end plate. Each Ach receptor has capacity to bind two Ach molecules in which case the receptor undergoes a conformational change to allow the passage of sodium and potassium ions, thereby generating an miniature end-plate potential (MEPP). If sufficient Ach-receptors are occupied, the end-plate potential will be sufficient to reach membrane threshold potential and lead to a propagated action potential. During this process calcium is released by the sarcoplasmic reticulum to interact with actin and myosin producing an all or none contraction of the muscle cell.

Ach is quickly hydrolyzed into acetate and choline, after its release by the action of a substrate specific enzyme called acetylcholinesterase (or simply cholinesterase). Eventually, once Ach is depleted the Ach receptor ion channels close, and the muscle cell membrane repolarizes. The intracellular calcium is then re-sequestered into the sarcoplasmic reticulum and the muscle cell relaxes.

All neuromuscular blocking drugs are quaternary ammonium compounds with at least one positive charged nitrogen atom that is bound to the alpha-subunit of post-synaptic cholinergic receptors. These drug compounds share similarities with the endogenous acetylcholine neurotransmitter molecule. Succinylcholine, a depolarizing muscle relaxant, is essentially two acetylcholine molecules linked over an ester bridge. Other neuromuscular blocking drugs, such as pancuronium, rocuronium or mivacurium, have a bulkier molecular structure. The molecular structures of these drugs are very important, as it impacts the characteristics of how they produce neuromuscular blockade.

Classes

Neuromuscular blocking agents are divided into two main categories: depolarizing and non-depolarizing. Each category is unique in its mechanism of action, response to peripheral nerve stimulation and reversal of blockade.

There are two broad categories of neuromuscular receptor blocking drugs:

1. Non-Depolarizing Agents: those agents that interact with the post-junctional receptor in such a fashion as to produce depolarization and muscular contraction before rendering the muscle cell inert. This type of block cannot be antagonized or reversed because the affinity of the agent for the receptor exceeds that of acetylcholine. Succinylcholine is the prototype depolarizing agent.
2. Depolarizing Agents: There are two chemical classes of depolarizing neuromuscular blocking agents:
    a. Benzlisoquinolines: Curare is the prototype
    b. Aminosteriods: Pancuronium is the prototype

    Because these agents possess similar affinity for the nicotinic receptor as Ach this block can be reversed by increasing the concentration of Ach at the motor endplate.

These two classes of medications possess different electrophysiological characteristics when subject to electrical stimulation. Electrical stimulation is employed to monitor a block.

Monitoring

This brings us to the important topic of evaluation of neuromuscular blockade. Currently, the most reliable and widely accepted method of intraoperative monitoring of neuromuscular blockade is via a peripheral nerve stimulator. The nerve stimulator provides electrical stimulation to a peripheral nerve, which will then evoke a response, depending on the level of paralysis. Use of a peripheral nerve stimulator allows titration of the neuromuscular blocking drug, ordinarily a nondepolarizing agent, to produce the desired clinical effect. Evoked responses from the peripheral nerve stimulator are used to judge spontaneous recovery from a neuromuscular blockade. At the end of a surgery, if the recovery is not adequate and is hindering spontaneous respirations, the recovery process may be accelerated by the administration of AcetylCholinEsterase inhibitor medications, such as neostigmine to increase the concentration of Ach at the motor endplate..

To actually use the peripheral nerve stimulator, small electrodes are placed either at the ulnar aspect of the wrist to stimulate the adductor pollicis, or over the facial nerve on the lateral side of the face. When the electrodes are placed, the nerve stimulator is used to deliver a supramaximal electrical stimulus. Of note, monitoring the response of the orbicularis oculi muscle to facial nerve stimulation is a better indicator of laryngeal paralysis than its ulnar counterpart. Furthermore, the onset of muscle blockade is quicker, but less intense at the level of the vocal cords vs. adductor pollicis when a non-depolarizing neuromuscular blocking agent is given. This means, that if one is monitoring only the adductor pollicis, relaxation of the cords may already be dissipated by the time maximal effect is seen at the ulnar nerve. This is in contrast to succinylcholine where relaxation at the level of the cords and the ulnar nerve follows a similar time course after administration.

Patterns of electrical stimulation used to assess the effects of a neuromuscular blockade include: single twitch response, train-of-four (TOF) ratio, double burst suppression, tetanus, and post-tetanic stimulation. TOF stimulation is the delivery of four 2Hz electrical stimuli 0.5 seconds apart. TOF stimulation is based on the idea that acetylcholine is depleted with successive stimulations. Tetanus is a continuous 50Hz stimulus delivered for 5 seconds. Blockade from non-depolarizing muscle relaxants produces a fading evoked response to tetanus stimulation; conversely, blockade by succinylcholine produces a reduced but not fading evoked response to tetanus stimulation – this is a phase I block.

A twitch response depression of >90% or elimination of 2-3 twitches out of the TOF is indicative of adequate relaxation for the purpose of an intra-abdominal surgery. If some twitches from a TOF stimulation are present it implies that antagonism of the blockade is likely to be successful.

The Agents

Let's discuss depolarizing agents first. Succinylcholine is the only clinically relevant depolarizing neuromuscular blocking agent. It is a depolarizing agent because it's long and flexible molecular structure allows it to bind and activate post-synaptic cholinergic receptors, thereby depolarizing the motor endplate. Like Ach, it is broken down by acetylcholinesterases, but because it is rather tightly bound by the receptor it's concentration in the synaptic cleft does not fall quickly. As the succinylcholine slowly dissociates from the nicotinic receptor is it metabolized by plasma cholinesterase and the block recedes over 8-10 minutes. This is called a Phase 1 block. Depolarizing blocks are characterized electrophysiologically as not demonstrating fade on train of 4 stimulation and

In some cases, very large doses of succinylcholine (usually in excess of 4 mg/kg) results in prolonged depolarization of the muscle end-plate, even though the remainder of the myocite membrane repolarizes. The result is a muscle cell that cannot be activated to contract. This is called a phase 2 block.

Depolarizing muscle relaxants do not exhibit any fade, or gradual reduction in evoked response during nerve stimulation, unless a Phase 2 has been produced, in which case the electrophysiological features resemble those of a non-depolarizing block.

There is no specific reversal agent for depolarizing muscle relaxants. Succinylcholine is the only muscle relaxant with a rapid onset and very short duration of action. This characteristic makes it a common emergency medication; it is often kept close by to ensure a patient can be quickly blocked, should the need arise for urgent intubation or to treat severe laryngospasm for example. The rapid onset and offset of the medication make it ideal for this emergency setting use.

Non-depolarizing muscle relaxants may be short-, intermediate- and long-acting. Since Ach is still prevented from binding to its receptor, no motor end-plate potential develops. Therefore, non-depolarizing muscle relaxants function as acetylcholine receptor competitive antagonists. A consequence of this type of blockade is the characteristic response to peripheral nerve stimulation. A non-depolarizing block generates a characteristic fade, that is a gradual reduction in evoked response during nerve stimulation. Absence of fade is a good clinical indicator of recovery from motor blockade.

Other than mivacurium, non-depolarizing muscle relaxants are not metabolized by acetylcholinesterase or pseudocholineterases. Reversal of non-depolarizing muscle relaxants depends on excretion, metabolism, redistribution of the agent or administration of specific reversal agents. Reversal agents, such as cholinesterase inhibitors, inhibit acetylcholinesterase enzyme activity; this increases the available acetylcholine pool available at the NMJ to compete with the non-depolarizing agent. This is in contrast to depolarizing muscle blockade, where administration of a cholinesterase inhibitor would prolong the depolarizing blockade.

Clinical Importance

The ability to produce skeletal muscle paralysis through the use of neuromuscular blocking drugs is clinically very important. A principal use of muscle relaxants is to facilitate endotracheal intubation. In addition to aiding with intubation, they also provide optimal surgical working conditions by producing relaxation of skeletal muscles such as abdominal muscles. Outside of the OR, neuromuscular blocking agents may be used in emergency departments or intensive care units to facilitate intubation, mechanical ventilation and patient management.

One very important fact to be aware of with neuromuscular blocking drugs however, is that they do NOT provide any anesthetic or analgesic effects. This is a common patient fear, publicized in films like *Awake*. It is a valid patient concern and one that should be recognized. An insufficient level of anesthesia in the paralyzed patient renders the patient at risk for awareness during a general anesthetic, a rare but exceedingly undesirable event.

Indications and Contraindications

Indications for neuromuscular blockade would include: need for endotracheal intubation, the need to complete any surgical procedure that requires skeletal muscle paralysis, or a need for mechanical ventilation.

Contraindications vary based on the type of blockade being used. In general however: any contraindication to the proposed surgical procedure, predicted difficult or impossible intubation, inability to provide adequate mechanical ventilation, major burns or digitalis toxicity, any neuromuscular disease (degenerative or dystrophic), spinal cord injury, severe trauma, severe cardiac arrhythmias, cholinesterase deficiency or family history of malignant hyperthermia (a contraindication for succinylcholine only), known myopathies or electrolyte abnormalities.

Complications

Complications secondary to neuromuscular blockade are dependent on the type of blocking agent used, namely depolarizing or non-depolarizing.

Succinylcholine is a relatively safe drug, with a few well-known complications, which should be understood and avoided. Because it's molecular structure so closely resembles the endogenous acetylcholine molecule, succinylcholine stimulates all Ach receptors, not just those at the NMJ. At the level of the heart, this muscarinic effect may result in cardiac dysrhythmias including sinus bradycardia, junctional rhythms, or sinus arrest. Fasciculation's, or visible motor unit contractions are often a visible sign of onset of paralysis induced by succinylcholine. Postoperative muscle pain occurs regularly following the use of succinylcholine but has not been related to the intensity of fasciculations, nor can it be prevented by pretreatment with a small dose of a non-depolarizer though this strategy does effectively attenuate visible fasciculations. Hyperkalemia is another side effect seen with succinylcholine administration; for this reason, it should be avoided in patients with already elevated potassium levels with signs on ECG of hyperkalemia. Fatal hyperkalemia has been reported following burn injury , massive crush injury, or patients with some neurologic disorders. Depolarizing muscle relaxants may also cause increased intragastric, intracranial and intraocular pressures probably related to the muscular fasciculations. Patients with low or abnormal types of pseudocholinesterase will have prolonged paralysis; this is important because in these cases adequate ventilation must be maintained mechanically till the block wears off. The final and most important potential complication from succinylcholine administration is development of malignant hyperthermia (MH). Succinylcholine is a potent trigger for patients susceptible to MH; paradoxical contraction of jaw muscles after succinylcholine administration may be the first sign of developing MH.

Non-depolarizing muscle relaxants on the other hand, have a separate list of potential complications that require consideration. However, because of the wide range in molecular structures of the non-depolarizing agents, the side effect profile is quite variable for each. Potential side effects include: tachy- or brady-cardia, bronchospasm, skin flushing, vasodilation and hypo- or hyper-tension. The antigenic quaternary ammonium group, common to all agents, is a potential risk factor for hypersensitivity reactions.

In Summary

1. Neuromuscular blocking agents are quaternary ammonium compounds that act on acetylcholine receptors at the neuromuscular junction to prevent skeletal muscle contraction
2. Neuromuscular blocking agents are divided into depolarizing and non-depolarizing. Non-depolarizing are further subdivided into short-, intermediate-, and long-acting.
3. Neuromuscular blocking drugs are vital for things like: intubation, intra-abdominal surgeries, and mechanical ventilation

4. Peripheral nerve stimulators are used to monitor the level of neuromuscular blockade; evoked responses from the facial nerve have greater correlation with larynx paralysis than the ulnar nerve
5. Complications vary based on which agent is used for muscle relaxation, of note succinylcholine is a potent trigger for malignant hyperthermia – a medical emergency
6. Indications and contraindications for neuromuscular blocking agents vary with the agent