NEUROMUSCULAR BLOCKING AGENTS

A LEARNING RESOURCE FOR INTENSIVE CARE NURSING STAFF

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Introduction:

- Neuromuscular blocking agents (NMBAs) paralyse skeletal muscles by blocking the transmission of nerve impulses at the myoneurol junction.

- NMBAs do not have sedative, amnesic or analgesic properties. For these reasons, adequate sedation and analgesia is essential prior to initiating therapy with NMBAs.

- NMBAs paralyse/relax the jaw and the vocal cords facilitating laryngoscopy and tracheal intubation, and various other muscles (especially of the trunk) whose paralysis may facilitate artificial ventilation and surgery.

- These drugs may be useful to improve patient-ventilator synchrony, enhance gas exchange, and reduce the risk of barotrauma.

- They can also be employed to reduce oxygen muscle consumption, facilitate short procedures, prevent unwanted movements in patients with increased intracranial pressure, and facilitate treatment of acute neurological conditions such as tetanus.

- When an NMBA is given, the patient’s capacity to respond by movement i.e. motor capacity is impaired or abolished, and it becomes difficult to assess if the patient is adequately sedated and/or free from pain. Unfortunately, indirect autonomic or involuntary responses such as an increase in heart rate, blood pressure or lacrimation, have all proved unreliable signs of consciousness, because they can also be influenced by other drugs e.g. vasoactives.

NMBAs are divided into 2 groups:

1. Depolarising agents
2. Non-depolarising agents

Depolarising agents:

- Suxamethonium is utilised to facilitate intubation.

- It has a rapid onset (less than 1 minute) and brief duration of action (7 to 8 mins).

- Its action cannot be reversed by the administration of other medications.

- Significant adverse effects include hypertension, tachycardia, bradycardia, ventricular arrhythmias, hyperkalaemia, and less commonly, increased intracranial pressure or malignant hyperthermia.

- Serum potassium concentrations increase by 0.5 to 1.0 meq/L due to an efflux of potassium from muscle cells. As a result, the drug must be used cautiously in patients with pre-existing hyperkalaemia.

- In thermal injury, there is an exaggerated release of potassium after administration of suxamethonium and profound hyperkalaemia associated with cardiac arrest may occur. Although the precise onset and duration of risk are not well described, the risk increases over the first few days following the injury.
Non-depolarising agents:

Non-depolarising NMBAs are structurally divided into the aminosteroid compounds and the benzylisoquinolines.

A number of non-depolarising neuromuscular blocking agents are available:

1. Atracurium (benzylisoquinoline)
2. Rocuronium (aminosteroid compound)
3. Vecuronium (aminosteroid compound)

The onset of action, half-life, and route of elimination are variable and drug-specific. The onset of action ranges from 1 to 5 minutes, but all are slower than suxamethonium. The action of non-depolarising NMBAs can be reversed by administration of an anticholinesterase drug such as neostigmine.

The action of the steroidal neuromuscular blocking agents such as rocuronium and vecuronium can be reversed by administration of suggamadex.

Atracurium:

- Is a benzylisoquinoline with an immediate duration of action.
- It does not require a dose adjustment in patients with renal or hepatic failure.
- However acidosis and severe hypothermia decrease the rate of drug metabolism and should prompt dose reduction. Specific dosing recommendations are not available, and the drug should be titrated according to neurological response.
- The major side effect associated with atracurium is hypotension caused by histamine release.

Vecuronium:

- Is an aminosteroid compound with an intermediate duration of action.
- It is hepatically metabolised to three active metabolites, all of which are eliminated by the kidney. Minimal adverse cardiovascular side effects have been reported.

Rocuronium:

- Is similar to but less potent than vecuronium.
- It has a rapid onset and short-to-intermediate duration of action.
- The drug is eliminated primarily by the liver and is associated with few adverse cardiovascular side effects.
Acetylcholine (ACh) is the neurotransmitter at skeletal muscle synaptic junctions. It is synthesized from choline and acetyl coenzyme A by acetylcholinetransferase and stored in presynaptic vesicles. An action potential causes influx of calcium ions at the nerve terminal, the vesicles then move into the active zone and fuse with the axonal membrane. The active zones lie opposite the postsynaptic membrane ACh receptors. An action potential causes 200–300 vesicles to release their quanta of ACh into the space between the nerve terminal and the muscle membrane (the junctional cleft) (Figure 12.1).

The ACh binds to the two alpha subunits of the ACh receptor, causing its ionophore to briefly open and allowing ion flux (mainly Na⁺ influx followed by K⁺ efflux). Spread of the action potential causes mobilization of Ca²⁺ from the sarcoplasmic reticulum and subsequent muscle contraction. ACh is metabolized by acetylcholinesterase, present in the junctional cleft (60 nm wide) and postsynaptic membrane junctional folds. The choline produced by ACh breakdown is taken up for reuse.
Clinical use:

- NMBAs are not 1st line agents for managing critically ill patients in the ICU.
- NMBAs are generally reserved for those with severe, refractory or life-threatening hypoxaemia (e.g. acute respiratory distress syndrome (ARDS) who are not responsive to other sedatives or analgesics.
- ICU staff must be trained in the administration of NMBAs.
- Appropriate airway control, mechanical ventilator support, and **adequate sedation and analgesia** are essential **prior to the initiation** of NMBAs therapy and **during** NMBAs therapy.
- Appropriate equipment for monitoring cardiorespiratory function and the capability of assessing the degree of muscular paralysis must be available.

Selecting an agent:

A patient’s renal and hepatic function, cardiovascular status and age must be considered when selecting an NMBAs agent.

- Hepatic and/or renal insufficiency – atracurium is preferred.
- Cardiovascular disease – vecuronium has the least adverse cardiovascular effects and is the drug of choice for patients with cardiovascular disease or haemodynamic instability. Rocuronium is an acceptable alternative.
- Elderly patients – drug selection is dictated by age-associated decreases in renal and hepatic function. Decreased cardiac output prolongs drug delivery and slows the onset of action of NMBAs.
- Obesity may also affect dosing requirements. Obesity does not appear to alter the pharmacokinetics of suxamethonium or rocuronium. This suggests that these agents can be dosed according to actual bodyweight rather than predicted bodyweight.
- In contrast, atracurium and vecuronium have a prolonged duration of action if they are dosed according to actual body weight.
- Given the variability among NMBAs and the overall paucity of dosing information from critically ill obese patients, there is a suggestion to start with low doses and titrating the dose using train-of-four monitoring.

Administration:

- NMBAs can be administered by continuous infusion or intermittent iv injection.
- Generally, long-acting NMBAs are best given by intermittent injection, while shorter-acting NMBAs are best given as a continuous infusion.
- Dose and frequency should be titrated to the desired clinical effect. Ideal or adjusted bodweight should be used for dosing obese patients.
Train-of-four monitoring:

- The depth of blockade should be assessed using a peripheral nerve stimulator every hour until the NMBA dose is stable.
- If no or 1 twitch is present: the dose should be reduced by 10%.
- If 3 or 4 twitches are present: the dose should be increased by 10%.
- Refer to learning resource for assessing depth of blockade.
- Some conditions interfere with the assessment of neuromuscular blockade e.g. Guillain-Barre syndrome, myasthenia gravis and critical illness polyneuropathy.

Daily discontinuation of NMBA for a few hours is recommended to:

1. Potentially decrease the incidence of prolonged recovery secondary to drug and metabolite accumulation.
2. To potentially decrease the risk of critical illness myopathy.

Tapering the dose is not necessary when NMB is discontinued. Sedation and analgesia adequate for patient comfort must be maintained as the NMBA is discontinued. In the context of end of life care, **NMBAs must always be discontinued** prior to withdrawal of ventilator support and **allow sufficient time** for the drug to wear off.

Patients receiving NMBA’s require meticulous care because the potential for complications is great. All paralysed patients require the following precautions:

- Ensure adequate sedation and analgesia **prior** to paralysing the patient.
- Explain all procedures to patients receiving NMBAs without general anaesthesia because **consciousness is not affected** by NMBAs alone. Reassure patient that communication abilities and muscle movement will return as the medication wears off. Regularly explain to the patient that the feeling of immobilisation is just temporary.
- **Assume pain is present** in patients that are pharmacologically paralysed. Administer pre-emptive opioid analgesia for common painful procedures e.g. turning/position change; tracheal suctioning; wound dressing changes; removal of wound drains.
- Careful **alignment** of head and neck. Regular passive limb movements. Regular change of position.
- Supervise patients closely because interruption of the ventilator circuit can be **fatal**.
- Since all NMBAs inhibit the cough reflex, **suctioning of the ETT** to remove accumulated secretions should be performed as needed based on the amount of secretions present.
- **Artificial tears** should be instilled every 2 to 4 hours and eyelids should be taped shut to prevent corneal drying and ulceration.
- 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.
What do patients experience?

NMBAs render a patient unable to move. If the patient is conscious they will be able to see, hear and feel but not respond. This ‘awareness’ is potentially extremely distressing and is associated with a high incidence of PTSD.

Experiences reported from patients (141 cases) that had received NMBAs:

- Inability to move 42%
- Inability to communicate 41%
- Hearing noise/voices 37%
- Touch without pain 21%
- Awareness of tracheal intubation 21%
- Pain 18%
- Inability to breathe or suffocation 11%
- Movement or being moved 9%
- Visual sensations 3%
- Dream-like experiences 5%

Commonly, patients find the experience of paralysis particularly disturbing and traumatic, may not appreciate its reversible nature, and have catastrophic appraisals about its cause and meaning.

The following patient reports are extracted from NAP5 Report and findings of the 5th National Audit Project: The Royal College of Anaesthetists – Chapter 7 Patient experiences and psychological consequences of accidental awareness during general anaesthesia. They provide insight into what some patients think and feel when they become aware of what is going on whilst “under the effects of anaesthesia”.

On waking in recovery an elderly patient reported having heard voices and feeling some pain. The following day the description became clearer and the patient described a sharp agonising pain of a knife slicing into skin and of flesh being pulled apart.

The patient tried to move but was unable to and was terrified of “enduring the torment”. The patient experienced flashbacks, reliving experiences and felt traumatised.

A patient recalled talk about hallucinations associated with ketamine, and then having their neck extended, a plugging sensation of something in the mouth and a suffocating feeling.

The patient tried to cry so that they could show people that they were awake. The patient recalled being positioned on the operating table and pain of the start of surgery.

The patient did not think they would survive. The patient developed PTSD with flashbacks, panic attacks, fear of the dark, and an inability to lie flat and was referred to a psychologist.

A patient reported for a few minutes hearing voices, and experiencing abdominal pain. The patient wanted to ask theatre staff to give painkillers but could not speak.

The pain was unpleasant; but the paralysis was not a great worry because the patient knew “you were supposed to be paralysed during the operation”. The patient was later not worried about having an anaesthetic.

Two patients thought they were actually dead at the time of the intra-operative awareness episode because of the experience of paralysis.

A patient reported neither pain nor the experience of being paralysed, but did report severe distress at “being alive only in the head”. The patient felt as if just their brain and ears were still working. “It felt like being in a crypt”. The patient could hear everything but felt no pain, only some touch when somebody lifted their leg, and something being drawn along the leg with a pencil (as did happen), some humming, and then with no pain, an incision. This case was associated with a psychotic episode post-operatively and PTSD.
GUIDELINES FOR USE OF THE PERIPHERAL NERVE STIMULATOR AND TRAIN-OF-FOUR MONITORING

INTENSIVE CARE UNIT RAIGMORE HOSPITAL

Indications for use:

- Long-term use of neuromuscular blocking agents (NMBAs) can result in prolonged neuromuscular blockade and skeletal muscle weakness.
- The objective of peripheral nerve stimulator assessment is to administer the smallest dose possible of the paralytic agent to avoid complications of prolonged weakness after therapy is discontinued.

Cautions:

- Patients with pacemakers and other specialised cardiac devices – discuss with medical staff.
- Do not apply to areas of skin inflammation or breakdown.

Preparing and connecting the peripheral nerve stimulator to the patient:

- The patient’s level of paralysis is carefully monitored using a peripheral nerve stimulator which delivers 4 identical stimuli in a row via skin electrodes, delivered as 2Hz.
- The preferred monitoring site is the ulnar nerve of either arm. This nerve controls the thumb, providing an observable contraction of the muscles in the thumb. When the nerve is stimulated with train-of-four (TOF) the expected response is 4 twitches i.e. in an individual that is not pharmacologically paralysed.
- Prepare the monitoring site by cleansing with an alcohol pad and dry. Remove any excess hair as necessary. Two skin electrodes are placed on the forearm over the ulnar nerve, proximal to the crease of the wrist and positioned approximately 2cm apart. The electrodes need to have good contact with the skin.
- The stimulator wires are then connected to the patient electrodes: the negative (black) lead is connected to the distal electrode and the positive (red) lead is connected to the proximal electrode. Ensure that the stimulator wires are correctly connected.
- Starting at the lowest setting, turn the intensity control clockwise, press the train-of-four switch and hold. At the same time observe the thumb for strong opposition i.e. movement of the thumb towards the palm of the hand.
- If thumb movements do not occur, check that the battery is functioning (replace the battery when it flashes deep red). Check that the amplitude/intensity setting is sufficient and repeat the TOF test. Check that the stimulator wires are correctly connected and securely connected to the electrodes.
- If no thumb movements are observed despite repeating the TOF test, discuss with medical staff as further medical assessment may be required.
Troubleshooting:

Estimating the degree of paralysis is not without problems. False positives may be recorded and may be due to the following:

- Inadequate skin preparation or poor skin contact with the electrodes.
- Oedema in the area being monitored.
- Improper electrode placement.
- Loose connection of stimulator leads.
- Stimulator malfunction such as battery depletion. Malfunction of the device can lead to over-estimation of the degree of blockade e.g. the patient may appear to demonstrate a 0/4 twitch response, but evidence of muscle movement is present.
- More problematic is the under-estimation of the degree of blockade. Direct stimulation of the muscle or mistaking finger responses instead of the thumb, can result in a false positive twitch response. This can lead to unnecessary administration of additional doses of the paralytic agent. It is important that the patient’s twitch response is correlated with clinical observations of the patient.
- Previous nerve injury may affect the results.
- Neuromuscular diseases e.g. Myasthenia Gravis, Bell’s Palsy and muscular weakness or paralysis may not respond normally to nerve stimulation.

Train-of-four monitoring:

- The number of twitches correlates to the level of paralysis.
- The goal being titration of the neuromuscular blocking agent to maintain 85-90% blockade, or 1 to 2 twitches out of 4 twitches i.e 1/4 to 2/4 twitches.
- Commence train-of-four monitoring 1 hour after initiating the neuromuscular blocking agent infusion.
- Perform train-of-four monitoring each hour and titrate the NMBA dose according to response. Titration may approximate 25 – 50%.
- Document the level of blockade on the patient’s monitoring chart and express as 0/4, 1/4, 2/4, 3/4 or 4/4.
- Inform medical staff if goal of 1/4 to 2/4 twitches is not achieved.
Train-of-four monitoring responses:

- 1/4 to 2/4 twitches: the goal of titrating the NMBA to maintain 85-90% has been achieved. Maintain current rate of infusion. Repeat TOF test hourly.

- 0/4 twitches: suggests that the level of paralysis is too high and the patient is at risk of developing complications of prolonged skeletal muscle weakness. The NMBA infusion rate should be reduced.

- 4/4 twitches: may suggest inadequate level of paralysis. If this is true, the patient is likely to demonstrate gag reflex on tracheal suctioning, or spontaneous respiratory effort may be observed on the ventilator. Refer to the troubleshooting suggestions above. If no thumb movements are observed despite repeating the TOF test, and no evidence of spontaneous muscle movement elsewhere, discuss with medical staff as further medical assessment may be needed.

Monitoring sites:

Ulnar nerve:

- Muscle involved is the Adductor pollicis.
- Action is adduction of the thumb.
- Black is positioned 1 to 2cm proximal to wrist crease.
- Red is positioned 2 to 3 cm proximal to black.
Facial nerve:

- Muscle involved is the Orbicularis oculi and Corrugator superciliii.
- Action is twitching of eyelid and eyebrow.
- Black is positioned just anterior to tragus. Position electrode by the ear lobe.
- Red is positioned to outer canthus of eye. Position electrode approx. 2cm from the eyebrow

Sural nerve (posterior tibial nerve):

- Muscle involved is the Flexor hallucis brevis.
- Action is plantar flexion or curl of big toe.
- Black is positioned over posterior aspect of medial malleolus. Palpate the posterior tibial pulse and place the electrode there.
- Red is positioned 2 to 3 cm proximal to the black.