Neuromuscular blocking agents (NMBAs) are one of the most commonly used classes of drugs in operating rooms and intensive care units (ICU). These agents are used to ensure muscle relaxation for periods of time ranging from a few minutes to a few days (1, 2). This review outlines the indications, classification, pharmacology, pharmacokinetics, adverse effects, complications, monitoring, blockade reversal, and criteria for selection.

**Indications**

NMBAs have a variety of indications for short and long term use in the ICU. The most common indication for NMBAs in the ICU is to facilitate mechanical ventilation. Hypoxic patients such as those with acute respiratory distress syndrome may require more than deep sedation to facilitate mechanical ventilation. NMBAs are given to prevent respiratory dysynchrony, stop spontaneous respiratory efforts and muscle movement, improve gas exchange, and facilitate inverse ratio ventilation. Furthermore, NMBAs are used to facilitate endotracheal intubation; the use of rapid acting and short duration NMBAs ease tracheal intubation by causing profound skeletal muscle relaxation. In addition, these agents allow the airway to be secured quickly. Also, NMBAs have a role in controlling intracranial pressure (ICP). It may help to attenuate transient elevation in ICP due to agitation, suctioning, and coughing in patients with elevated ICP. Additionally, NMBAs have been used to reduce muscle rigidity in tetanus, neuroleptic malignant syndrome, and status epilepticus. Finally, NMBAs are often used in minor surgical procedures like trachostomy, bronchoscopy, and surgical relaxation in patients where sedation alone does not abolish patient movement in order for the procedure to be completed (3,4).

**Classification of Neuromuscular Blocking Agents:**

Neuromuscular blockers come in two forms, depolarizing and nondepolarizing. In the depolarizing category, the only drug used in the United States is succinylcholine. Non-depolarizing neuromuscular blocking agents can also be classified to aminosteroidal compounds which include pancuronium, pipercuronium, vecuronium, and rocuronium, and benzylisoquinolnium compounds that include atracurium, cisatracurium, and doxacurium (3, 5).

**Depolarizing Agents: Succinylcholine:**

Succinylcholine, the only depolarizing agent currently used in clinical practice. Succinylcholine acts at the nicotinic receptor in biphasic manner. First it opens the sodium channel associated with nicotinic receptor which results in depolarization of the receptor (phase I) and leads to transient twitching of the muscle (fasciculation). With time, the continuous depolarization gives away to gradual repolarization as the sodium channel closes or is blocked which causes a resistance to depolarization (phase II) and flaccid paralysis (3).

Succinylcholine has a favorable pharmacokinetic profile; it has a rapid onset (30-60 seconds) and short duration (5-15 minutes). These two features make it the ideal drug for use in endotracheal intubation. Additionally, it is rapidly hydrolyzed by plasma and hepatic pseudocholinesterase (5).

Administration of succinylcholine is associated with a number of adverse effects such as hyperkalemia, bradycardia, malignant hyperthermia, and muscle rigidity. A life threatening increase in serum
potassium has been observed in a number of patients after the administration of succinylcholine and fatal outcomes are well documented. Hyperkalemia may be exaggerated in patients with burns, rhabdomyolysis, crush injuries, intra-abdominal infections, sepsis, spinal cord injuries, and neuromuscular disorders.

Bradycardia is the most commonly observed succinylcholine dysrhythmia with rare reports of asystole and ventricular tachycardia. The incidence of dysrhythmia is increased in pediatric and adult patients after multiple doses of succinylcholine. Premedication with atropine 0.4 mg IV in adults prior to a second dose of succinylcholine may prevent dysrhythmia.

Succinylcholine administration occasionally triggers malignant hyperthermia with muscular rigidity and hyperpyrexia which is a rare complication that most often occurs in genetically susceptible individuals and it has been reported following the administration of halothane and succinylcholine. Malignant hyperthermia can be managed by rapid cooling and administration of dantrolene which blocks the release of calcium from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone. A previous history or family history of malignant hyperthermia is an absolute contraindication to the use of succinylcholine.

Another adverse effect of succinylcholine is muscle soreness that can occur 24-48 hours after administration and can be a source of significant discomfort for the patient. It also increases both intraocular and intracranial pressure; however, these effects are transient and clinically unimportant. Succinylcholine also has been observed to induce histamine release which may result in transient hypotension and bronchospasm.

Nondepolarizing Agents:

The nondepolarizing NMBAs include many agents such as pancuronium, pipercuronium, vecuronium, rocuronium, atracurium, cisatracurium, doxacurium, and mivacurium. These agents at low doses bind to the nicotinic receptor and prevent the depolarization of muscle cell membrane and inhibit nicotinic contraction. Since these agents at low concentration compete with acetylcholine at the receptor, they are called competitive blockers. Their action can be overcome by increasing the concentration of acetylcholine at the post synaptic receptor, as demonstrated by cholinesterase inhibitors such as neostigmine or edrophonium.

At high doses nondepolarizing NMBAs block the ion exchange at the endplate of the synapse which leads to further weakness of neuromuscular transmission and reduces the ability of cholinesterase inhibitors to reverse the action.

Pancuronium is a long acting aminosteroidal nondepolarizing NMBa with a peak effect occurring within 2-3 minutes and duration of action of 60-90 minutes. Approximately, 30-45% of the drug is metabolized in the liver, producing at least one metabolite 3-desacetylpancuronium with neuromuscular blocking activity. The rest (55-70%) is excreted unchanged in the urine.

Pancuronium is also vagolytic; more than 90% of the ICU patients will have increase in heart rate of ≥ 10 beats/minutes. Pancuronium’s neuromuscular blocking effects are prolonged in patients with renal failure or hepatic dysfunction due to an increase in half-life and a decrease of its active metabolite.

Pipercuronium is another long acting nondepolarizing agent similar to pancuronium in structure, pharmacological activity and pharmacokinetics. Neuromuscular blockade is generally observed within 2-3 minutes and lasts for 80-100 minutes. The elimination half-life is around two hours with 40% of the drug excreted unchanged in urine.

Vecuronium is an intermediate acting NMBa that is a structural analogue of pancuronium. It produces blockade within 2-3 minutes and typically lasts for 20-30 minutes. Its duration may be prolonged in patients with renal impairment as up to 50% of the dose is excreted unchanged in urine. Likewise, 50% of the dose is excreted in bile and patients with hepatic dysfunction will need dosage adjustment to maintain adequate blockade. Vecuronium causes virtually no vagolytic or hemodynamic alterations.

Rocuronium is a monoquaternay steroidal intermediate acting NMBa with an onset of action of 1-2 minutes and duration of 30-60 minutes. Its rapid onset of action and intermediate duration make it potentially an important agent for use in rapid sequence intubation. It causes minimal homodynamic alterations and no histamine release.

Atracurium is an intermediate acting NMBa that has minimal cardiovascular effects and at higher concentrations is associated with histamine release. It is inactivated in plasma by ester hydrolysis.
and Hoffman elimination. Laudanosine is a breakdown product of Hoffman elimination of atracurium and has been suspected to have central nervous system excitatory properties as it precipitates seizures in patients with hepatic failure or who are receiving high doses of atracurium (3). Flushing, peripheral vasodilatation, decrease in mean arterial blood pressure, and wheezing are the most common adverse effects related to atracurium histamine release (8).

Cisatracurium is an intermediate acting benzylisoquinolnium nondepolarizing NMBA. Cisatracurium undergoes Hoffman degradation and ester hydrolysis and the duration of blockade is not affected by renal or hepatic dysfunction. Cisatracurium produces fewer cardiovascular adverse effects and has fewer tendencies to produce mast cell degranulation (11).

Doxacurium is a long acting benzylisoquinolnium agent. It has high potency and is devoid of hemodynamic adverse effects (3, 10). It is primarily eliminated renally and a significant prolonged effect may occur in elderly patients with renal impairment. Mivacurium is the only nondepolarizing agent classified as short acting. It has a half-life of two minutes which allows rapid reversal of blockade (3,10). Mivacurium administration may result in histamine release and concomitant hypotension and tachy-cardia (8). It is considered an appropriate choice for emergent neuromuscular blockade when succ-inylcholine is contraindicated.

Monitoring:

Neuromuscular blockade should be monitored in all patients who receive long term therapy. The goal of monitoring the degree of neuromuscular blockade is to provide the lowest dose of NMBA and minimize adverse effects. The three methods which are commonly used to monitor NMBA are: visual, tactile, or electronic assessment of a patient’s muscle tone or combination of the above mentioned methods. Peripheral nerve stimulation where a series of electrical stimuli to a nerve and the muscle response is observed or measured is the recommended method to monitor paralysis (3, 4). Train of Four (TOF) is four consecutive stimuli delivered along the path of a nerve (low frequency 2-4 Hz for 2 seconds at 0.5 second intervals) and the response of the muscle is measured in order to evaluate stimuli that are blocked versus those that are delivered (4, 7). Avoidance of deep blockade (zero of four twitches) is recommended. Patients should always have at least one twitch present during infusion or before redosing with intermediate acting NMBA (4, 7).

Consideration in NMBA Selection:

Factors which influence the selection of an ideal NMBA are cardiovascular stability, speed of onset and offset required, possible accumulation of the NMBA metabolites, elimination routes, and cost (4).

Reversal of Neuromuscular Blockade:

The action of NMBA can be reversed either spontaneously as result of the decrease the concentration of the agent or by reversal with acetylcholine cholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Neostigmine is the most commonly used agent in the ICU (7). The major toxic effect of these agents is muscarinic stimulation which results in severe bradycardia and salivation. Pretreatment with anticholinergic drugs like atropine or glycopyrrolate may block the muscurinic effects (7).

Conclusion

Although NMBA are one of the most commonly used classes of drugs, the decision to administer neuromuscular blocking agents to patients in the ICU should be based on the consideration of individual patient characteristics, and a detailed knowledge of the pharmacokinetics, and the adverse effects of these agents together with the type of anesthesia to be used.

References