The author provides a review of the mechanism of neuromuscular transmission, as well as the mechanism of action and differences between curare and succinylcholine.

Effects of these two relaxants on various organs and tissues are discussed, as are their onset of action, duration, elimination, and clinical uses.

In order to understand how skeletal muscle relaxants act, the mechanism of neuromuscular transmission must first be understood. By way of review, a nerve impulse consists of action potential electrical current. When this action potential arrives at the terminal membrane of the axon, it causes release of the quaternary base acetylcholine from its storage protein at the membrane into the subsynaptic space which is part of the extracellular space. This space is rich in sodium ions. Once in the subsynaptic space, acetylcholine crosses to the post-junctional membrane or more specifically, the end-plate region of the muscle membrane and becomes adsorbed to cholinergic receptors in the membrane.

The post-junctional membrane is semi-permeable and prevents migration of sodium ions in and potassium ions out. Sodium predominates outside the membrane and potassium and other large impermeable anions predominate inside. At rest, uneven distribution of ions causes the outside to be positively charged while the interior is negative. The potential difference is called the resting potential.

The cholinergic receptors in the post-junctional membrane contain proteins and when acetylcholine is adsorbed by these proteins, their molecular configurations are changed. The pore size and permeability of the membrane is also changed. This causes the membrane to become depolarized.

During the depolarization process, sodium migrates in and the potassium migrates out. Sodium moves in faster than potassium or chloride ions move out. The negative potential is reduced at first to -45 millivolts which results in end-plate potential. With further decrease to zero and an overshoot to +30 millivolts, an action potential results. The exterior of the membrane becomes negative and the interior becomes positive. The action potential spreads through the muscle fiber and contraction results. A lag of 2 or 3 milliseconds precedes contraction. The time of muscle contraction may take approximately 200 milliseconds.

The resting potential at the motor end-plate is restored much faster than the time it takes for muscle contraction. Acetylcholinesterase, which is present in protein in the junctional membrane, becomes active and hydrolyzes acetylcholine into acetic acid and choline. This takes approximately .1 millisecond. This restores permeability to the post-junctional membrane so that it becomes positive and the interior becomes negative. The negative resting potential of -90 millivolts is re-
stored and the membrane is ready for the next nerve impulse. The process is capable of repeating itself several hundred times per second. Choline acetylase, which is stored on a special protein and released, resynthesizes acetylcholine from acetic acid and choline and reunites it with the storage protein in the terminal membrane of the axon. The process takes about 0.1-0.2 milliseconds.

Non-depolarizing muscle relaxants

Changes at the neuromuscular end-plate region caused by non-depolarizing muscle relaxants. Non-depolarizing muscle relaxants prevent access of acetylcholine to the receptor protein. They have an affinity comparable to that of acetylcholine for receptor sites so the law of mass action applies. This results in no depolarization and prevents a change in resting potential of the motor end-plate. The result is no muscular contraction or paralysis. Non-depolarizing relaxants do not cause muscular fasciculation.

Factors that enhance non-depolarizing muscle relaxants. Paralysis is increased when using either non-depolarizing or depolarizing relaxants by such things as halogenated volatile anesthetic agents, ether, lidocaine, digitalis glycosides, quinidine, diuretics, and procaine. Non-depolarizing blocks are also increased by additional non-depolarizers. Respiratory acidosis (PaCO₂ greater than 50 torr) enhances non-depolarizing blockade by limiting and blocking its antagonism. If a residual curare blockade occurs in a patient in the recovery room and his PaCO₂ is building up due to hypoventilation, it may be difficult to reverse the blockade. Narcotics given to relieve pain in the recovery room may increase the likelihood of this happening.

It would seem likely that metabolic acidosis would also increase the chances of enhancing blockade but it has not been substantiated. It has been shown that metabolic alkalosis has prevented neostigmine antagonism of curare. In studies done by R.D. Miller and associates, it was shown that extracellular H+ concentration (pH) per se may not have been as important as changes in electrolytes and intracellular pH.

Dehydration, which causes a deficiency of extracellular potassium, enhances the block from non-depolarizing relaxants and diminishes the ability of neostigmine to antagonize the block. This is due to an increase in end-plate transmembrane potential because of a higher ratio of intracellular to extracellular potassium.

Antibiotics, such as neomycin, streptomycin, kanamycin, and polymyxin, if given parenterally or intraperitoneally, may cause a non-depolarizing block which will be enhanced by non-depolarizing drugs such as tubocurarine. The block can be reversed by neostigmine. The end-plate membrane potential is dependent on the presence of calcium ions, and this is reduced by the antibiotics.

Factors that antagonize non-depolarizing relaxants. Non-depolarizing blockade is decreased by anticholinesterase drugs such as neostigmine, depolarizing drugs, adrenaline, and acetylcholine. A low body temperature decreases the degree of block, but not its duration. Excess potassium ions also antagonize a non-depolarizing block.

Effects on cholinesterase. Acetylcholine continues to form and be hydrolyzed by cholinesterase without interference by the non-depolarizers. Muscle fiber responds to electrical stimuli and contracts when the stimulus is applied beyond the post-junctional membrane.

Reversal of non-depolarizing relaxants. Anticholinesterases or anticholine agents permit acetylcholine to accumulate and overcome non-depolarizing blocks by displacing the relaxant from the receptor sites. They do this by preventing cholinesterase from breaking down acetylcholine. Large doses may cause excess acetylcholine to accumulate which can enhance blockade by causing persistent depolarization.

Neostigmine, an anticholinesterase, can be used to reverse a curare block. The usual dosage is 1.5-2.5 mg intravenously. Since it has parasympathomimetic actions, it can cause a pronounced bradycardia. For this reason, atropine is given with neostigmine to counteract the bradycardia. The usual dosage of atropine is 0.6-1.0 mg intravenously.

Curare

Effects on the neuromuscular junction. D-tubocurarine, hereafter known as curare, is a non-depolarizing muscle relaxant and acts by competitive inhibition of acetylcholine. It has no action of its own but prevents acetylcholine from attaching to the cholinergic receptors on the post-junctional membrane by attaching itself to the receptors. It does not inhibit acetylcholine formation at the nerve ending and it does not inhibit activity of cholinesterase. As mentioned earlier, muscles respond to direct electrical stimulation because depression occurs at the end-plate. Curare does not penetrate muscle fiber and exerts no action on smooth muscle.

Effects on various organs and tissues. Curare causes some depression of the cerebrum with paralytic doses but subparalytic doses cause no depression. Memory, perception of pain, and other cere-
bral reactions remain active. There may be a fall in body temperature with its use but this can be attributed to decreased motor activity and not to any effects on the temperature regulating center per se. Decreases in blood pressure are due to ganglionic blockade caused by large doses of curare and histamine release which causes a vasodilatation. With therapeutic doses, there are no significant effects on pressure.

The vomiting center is not depressed and involuntary muscles involving emesis remain active in unanesthetized patients. Paralysis affects the intercostal muscles before it affects the diaphragm. With curare, the diaphragm is the last voluntary muscle to be paralyzed and the first to recover. Curare has no effect on the pupils. The muscles of the eyeballs and lids are the first to be affected. Diplopia, ptosis, nystagmus, and heaviness of the lids will be experienced by the patient. (The patient should be forewarned of this if curare is used as a defasciculating agent prior to the use of succinylcholine).

There is relaxation and cessation of eyeball movements in the anesthetized patient. The facial nerve is the next to be affected. It causes a mask-like expression on the face. There is no effect on the salivary glands, and secretions continue to form. The gag reflex is abolished due to loss of motor control of the pharyngeal muscles. Coughing is abolished due to loss of expulsive power from paralysis of the thoracic muscles. There are no significant direct effects on the heart, and curare does not prevent dysrythmias. The muscle tone and peristalsis of the stomach and intestines are decreased.

Onset of action and duration. The onset of action of curare, when given intravenously, is within three minutes. The duration varies. A curarizing dose produces an effect lasting 25-30 min in a non-narcotized patient. In an anesthetized patient, the effect may last up to 1 hour.

Elimination. The liver partly detoxifies curare. The metabolism in the liver is slow because of a lack of lipophilic qualities and difficulty in passing through lipid membranes of liver microsomes. The remainder is eliminated unchanged by the kidney. It is believed by some that curare is less dependent on kidney function for elimination and is the preferred non-depolarizer in patients with renal failure.  

Clinical uses. Curare can be used to make endotracheal intubation by direct route relatively easy and atraumatic by removing the tone of cords and neck muscles. It is also used to aid muscular relaxation during anesthesia. It may be used to lessen laryngeal spasm and quiet upper respiratory reflexes during anesthesia and to facilitate control of respiration. Curare facilitates bronchoscopy and esophagoscopy procedures by depressing laryngeal reflexes. A combination of local anesthetic and curare in small doses of 0.1 mg/kg will produce an almost complete paralysis of the external eye muscles without affecting the ventilatory muscles to any serious degree; thus, such a combination is good for many types of eye surgery.

Curare can also be used in other surgical procedures considered in the middle range of time lasting 20-30 min. The intensity of muscular contractions seen in electroconvulsive therapy can be reduced by the use of small doses of curare. Curare can be used to prevent shivering during induction of hypothermia, although the block will be prolonged due to the decrease in body temperature. However, the block will not be as prolonged as a block induced by pancuronium.  

As a diagnostic test for myasthenia gravis, approximately 0.02-0.04 mg/kg of curare can be injected intravenously. If myasthenia is present, a marked exaggeration of its symptoms is produced in a minute or two. These symptoms can be reversed by the immediate intravenous injection of neostigmine and atropine.

Contraindications. Because of the marked increase in symptoms, curare and other non-depolarizers are absolutely contraindicated in known myasthenics. Other contraindications are severe shock from trauma or hemorrhage because of the possibility of decreased blood pressure, renal disease, or dehydration accompanied by electrolyte imbalance. Potassium deficiency (as mentioned earlier) potentiates action and those with hypokalemia should not be given curare.

Curare is also known to cause histamine release and patients with known bronchial asthma or other forms of allergies should not be given curare because it may induce severe bronchospasm or constriction. Also, as mentioned before, is the fact that antibiotics, especially the neomycins, may produce non-depolarizing type blocks; and non-depolarizers, such as curare, may be potentiated by these drugs. Therefore, patients on these drugs will require much less relaxant than normally required.

Advantages. Curare allows relaxation without having to deepen anesthesia. It allows light planes of anesthesia to be maintained with all agents. Halothane and enflurane, both potent agents, can be used in upper planes, thus avoiding dysrhythmias. With curare, relaxation can be obtained quickly within a few minutes after administration.
plus, there is no intolerance to repeated use. However, subsequent doses have a greater effect than the initial dose. Approximately one-third to one-half the initial dose is recommended when repeated.

Tachyphylaxis does not develop with the use of non-depolarizers. The placenta forms a relative barrier to the passage of muscle relaxants (depolarizers as well as non-depolarizers). The poor passage is due to poor penetrability, low lipid solubility, and a high degree of ionization.

Disadvantages. Paralytic doses of curare can cause death by asphyxia, so its use should be restricted to experienced anesthetists who are fully competent to institute and maintain efficient artificial respiration in all types of patients. Antidotes are not always effective when the patient is highly overdosed. Cumulative effects follow repeated doses and the action is prolonged. Curare is not effective when administered orally.

Dosages. On the average, 6-10 mg of curare causes limb paralysis without greatly reducing respiratory efficiency, and 15-20 mg causes paralysis of abdominal muscles. Usually, 20-30 mg is required for tracheal intubation. Infants and children tolerate the drug well. An average dosage is approximately 0.3 mg/kg of body weight.

Succinylcholine

Mechanism of block. The depolarizing muscle relaxant succinylcholine acts by depolarizing the motor end-plate of the neuromuscular junction. Succinylcholine does not prevent or enhance the release of acetylcholine. Instead, it permits uninterrupted liberation. It has the same action as acetylcholine in that it reacts with the receptors at the end-plate region of the muscle, leading to depolarization of the chemically excitable membrane. Influence is also exerted on the muscle fibers next to the end-plate making them unexcitable.

The block, however, is not at the end-plate as it is with non-depolarizers. Rather, it is in the area of the electrically excitable membrane around the end-plate. Fasciculation of the muscle bundles occurs because of the depolarization, especially in the neck and limbs, and is seen after rapid injection. It causes postoperative achiness, especially in ambulatory patients.

Succinylcholine, unlike acetylcholine, is not almost instantly hydrolyzed so depolarization remains and the muscle fibers remain unexcitable. Shortly after intravenous injection, muscular twitching occurs. This soon passes and gives way to muscular relaxation. Relaxation lasts for approximately three to five minutes after which muscular control returns rather rapidly. This is known as a phase I block. Repeated doses do not cause repetition of fasciculations.

After prolonged use, a phase II block may occur. Succinylcholine then acts like a non-depolarizer, and non-depolarizers reinforce the effect. Anticholinesterases antagonize phase II blocks but not phase I. Repeated doses or prolonged use may cause an abnormal state of the muscle, which leads to a diminishment of the ionic gradient and permeability. The membrane is then unable to give rise to an action potential. This may be the cause of the phase II non-depolarizing type block, though the exact cause is unknown.

Effects on various organs and tissues. Succinylcholine does not depress the cerebrum. Sensorium remains clear in the unanesthetized patient. The temperature regulating center is not affected but a fall in body temperature is due to decreased muscle activity. The respiratory center is not affected and apnea is due to peripheral blockade of respiratory muscles. The vagus center is not affected. The bradycardia sometimes observed is caused by peripheral stimulation of vagal ganglia.

There is no effect on the pupils. Intraocular tension can be increased due to extraocular muscles developing a tetanic state constricting the eyeball. The salivary glands continue to secrete, and the amount may even be increased. The gag reflex is abolished due to loss of motor control of the pharyngeal muscles. Sensory effects of the larynx are not affected, but laryngeal spasm can be relieved quickly by intravenous use of succinylcholine. There is no effect on the myocardium and the drug does not cause or prevent dysrhythmias.

It does not sensitize automatic tissues to catecholamines.

Vagal stimulation causes bradycardia after successive repeated doses. Large doses can cause transient elevations in blood pressure possibly due to ganglionic stimulation. Hypotension is uncommon except in massive doses which cause ganglionic blockade. The diaphragm is more resistant than other muscles, and is the first to resume activity after total paralysis.

Elimination. About 85% of succinylcholine is rapidly destroyed in plasma by the pseudocholinesterase which is produced in the liver. Hepatic diseases cause a decrease in pseudocholinesterase which may be responsible for prolonged apneas. The remaining 15% of the drug is excreted into the urine by glomerular filtration. The action is prolonged in renal insufficiency due to slow excretion.

Clinical uses. Succinylcholine is used clinically for endotracheal intubation. The usual dosage is
from 40-100 mg given as a bolus intravenously. To overcome acute laryngospasm, 50 mg can be injected intravenously followed by rapid intubation. For procedures such as bronchoscopy, esophagoscopy, and the like, it can be given in small serial doses. A moderate dose of pentothal, followed by 50-60 mg of succinylcholine, can be used for orthopedic manipulations.

The continuous drip of succinylcholine is used as a controllable and rapid method of maintaining relaxation of different degrees during short surgical procedures where the longer acting non-depolarizers would be a definite disadvantage. Patients who are in a debilitated or dehydrated state are especially sensitive to all muscle relaxants. The best relaxant to use is one of short duration. Postoperative hypoventilation should be minimal. Succinylcholine would be an excellent choice in situations like this.

The dangers of increased serum potassium. All of the depolarizing neuromuscular blocking agents cause elevation of serum potassium of 0.5-1.0 mEq/L in normal man.9 There is a marked rise of serum potassium in clinical situations where extensive denervation of skeletal muscle has occurred or where massive tissue trauma has taken place.11 Patients with extensive burns are particularly vulnerable to massive potassium shifts especially 5-7 days post-trauma. In these situations, the serum potassium may reach 5 mEq/L within a very short time. The myocardium may not be able to tolerate such shifts, especially the diseased heart. Ventricular arrhythmias and fibrillation are not uncommon. Succinylcholine should not be used in situations like these.

The cautious use of succinylcholine should be practiced in situations where the threshold of cardiac muscle to depolarization is lowered (as above). Other such situations include patients receiving catecholamines or tranquilizers that are mono-amine oxidase inhibitors. Reserpine (a catecholamine depleting drug) or alphamethyldopa eventually lower the threshold of excitability of adrenergic receptors. Exogenously administered catecholamine, or suddenly increased serum potassium levels caused by depolarizing agents such as succinylcholine, may interact with these types of drugs and may induce ventricular arrhythmias. A small dose of curare, such as 3-6 mg, before the administration of succinylcholine, will make the occurrence of cardiac arrhythmias less likely.

Other contraindications and cautions in the use of succinylcholine. Succinylcholine stimulates cholinergic sites such as autonomic ganglia and muscarinic receptors which lead to increases in intraocular and intragastric pressures. In patients with penetrating eye wounds, succinylcholine should not be used due to the possibility of loss of vitreous humor. However, succinylcholine is not contraindicated in patients with glaucoma for endotracheal intubation because the rise in intraocular pressure is only transient.

When there is the possibility of regurgitation from a full stomach, a defasciculating dose of curare or another non-depolarizer should be given prior to succinylcholine to lessen the chance of regurgitation from increased intragastric pressure. The frequent bradycardia and hypotension observed in children after the administration of succinylcholine can be prevented by the prior use of atropine. It is also known that single doses of succinylcholine can cause myoglobinuria. However, what is remarkable is that this occurs principally with halothane anesthesia.

Myasthenic patients under treatment with anticholinesterase agents will have a markedly prolonged response to succinylcholine. It should be avoided in these patients unless they have not received their anticholinesterase medication for 12 hours.

Succinylcholine use in patients with muscular dystrophies and myotonias should be avoided. The administration of succinylcholine results in prolonged action and aggravation of muscular dystrophies. In states of myotonia, it may produce an exaggeration of the muscle tone of all skeletal muscle.

Patients with a familiar history of malignant hyperthermia should definitely not be given succinylcholine, as this may trigger a hyperthermic reaction.

Plasma cholinesterase or pseudocholinesterase hydrolyzes succinylcholine, giving it its short duration of action. Occasionally, some patients exhibit low levels of this enzyme. This can occur after therapeutic radiation, after contamination with organic phosphorus insecticides, in hyperpyrexia, in cardiac failure, in uremia, in liver disease, in malnutrition, and in severe anemia. It is found as a familial abnormality in about 1/8000 of the population. When low levels of pseudocholinesterase are discovered, succinylcholine should be avoided due to the prolonged effect.

Dosage. When succinylcholine is used for endotracheal intubation, reduction of fractures, and for various short procedures, its amounts vary in range from 0.25 to 0.6 mg/kg, in single bolus, intravenous doses. Initial doses of 20-60 mg will produce surgical relaxation, with 30 mg being the
average. If this is inadequate, a second identical dose can be administered safely.

Following these doses, paralysis will occur within 60 sec and last 1-4 min. Larger doses may prolong apnea from 2-10 min. For intubation, the average dosage is 0.8 mg/kg. Up to 100 mg in the average adult can be given safely for this procedure. To avoid fasciculation and the danger of increased intragastric pressure (which may lead to regurgitation in a patient with a full stomach), a defasciculating dose of curare (3 mg) may be given approximately 3 min prior to the administration of succinylcholine.

When short procedures are unexpectedly prolonged, intermittent fractional doses may be given after the initial loading dose. These are given every 3-5 min, and each subsequent dose should be one-half the previous dose. This practice should not be extended for over 30 min; the relaxation is uneven.

Succinylcholine can be given as a continuous intravenous drip. This provides a greater margin of controllability in prolonged cases. The solution is a 0.1% concentration in 500 ml of 0.9 normal saline solution. The solution is titrated against a particular response. For induction of relaxation, a rate of 50-150 drops/min is maintained. This is equal to 5-10 mg/min and is run for 2-5 min. Apnea and relaxation occur in 2-4 min.

For maintenance, the dose depends on physical status, size, and pseudocholinesterase levels in the patient. An average of 2.5 mg or approximately 30 drops/min results in optimal relaxation in healthy patients.8

With subsequent doses or continuous drip infusion, succinylcholine decreases in action but the time of relaxation increases. Development of end-plate resistance to depolarization may be the cause of tachyphylaxis and desensitization (the phase II block mentioned earlier).

Intramuscular administration of succinylcholine is recommended for infants and children. The dosage is 4 mg/kg. When given intramuscularly or subcutaneously, 3-6 times the intravenous dose is required to get an equal effect.

When using succinylcholine other than for endotracheal intubation, some degree of spontaneous respiratory activity should be maintained so that the anesthetist is able to determine or evaluate the degree of muscular block. This can be aided by the use of a nerve block stimulator.

The disadvantages of muscle relaxants in use today and improvements for the future. The problem with depolarizing muscle relaxants, namely succinylcholine, is that they are of short duration and have a number of significant side effects. Non-depolarizers do not have these side effects, for the most part, but they are of long duration and must be reversed with anticholinesterases. The ideal muscle relaxant would be one that would develop a non-depolarizing block of varying length so that the anesthetist could choose according to the length of the procedure.

Another problem, obviously, with all muscle relaxants, is that of apnea. No relaxant reacts specifically at certain cholinergic receptors of certain muscle groups. If it could be understood (1) how the molecular configurations of the proteins attached to these receptors were changed when acetylcholine becomes adsorbed to them and (2) why the pore size and permeability of the membrane changes thus causing the membrane to become depolarized, it might be possible to avoid apnea and still have muscular relaxation.

If it were shown that these receptors differed only in minute ways, then relaxants could be developed that might affect only abdominal muscles or others and give relaxation while not affecting the muscles of respiration. This would be of great benefit to the future anesthetist.

REFERENCES


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