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Module1 INTRODUCTION TO NEUROMUSCULAR BLOCKERS

Module2 STRUCTURE ACTIVITY RELATIONSHIP

Module3 MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS (DRUGS)

Module4 CLASSIFICATION

Module5 DEPOLARIZING BLOCKING AGENTS

So, let's begin with our first module

Module1 INTRODUCTION TO NEUROMUSCULAR BLOCKERS

Drugs that relax skeletal muscle are called skeletal muscle relaxants, these agents are classified according to their use and mechanisms of action. These agents produce muscle paralysis required for surgical procedures and hyperactivity. Neuromuscular blocking agents block the transmission of acetylcholine at the motor end plate so consider as nicotinic antagonist. The therapeutic use of these compounds is primarily as adjuvants in surgical anesthesia to obtain relaxation of skeletal muscle. They are also used in various orthopedic procedures, such as alignment of fracture and correction of dislocation. The neuromuscular junction consists of the axon imposing onto a specialized area of the muscle known as the muscle end plate. The nerve terminal is separated from the end plate by a gap of 200 Å.

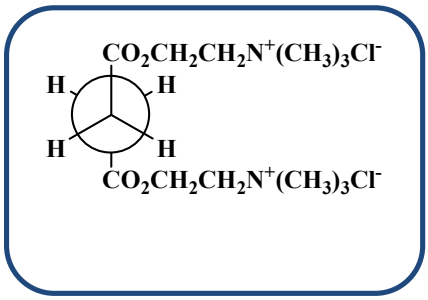
Uses of Neuromuscular blocking drugs

1. Endotracheal intubation.
2. Reduce muscle contractility and depth of anesthesia required for surgery.
3. In the intensive care unit to prevent high airway pressures, decrease O_2 consumption, and abolish muscle rigidity in patients on mechanical ventilation.
4. Reduces the chances of bone fractures during electroconvulsive therapy.

Module2 STRUCTURE AND STRUCTURE ACTIVITY RELATIONSHIP OF NMBDs

1. All the NMBDs available are quaternary ammonium compounds. The type of alkyl carbon (methyl, ethyl) indicates the charge distribution and binding characteristic of onium compounds.

2. Non-depolarizing drugs are generally bulky and more rigid than depolarizing drugs.
3. As the steric hindrance to receptor increases the potency decreases.
4. l- Tubocurarine is comparatively less potent than d-tubocurarine.
5. The depolarizing agents (decamethonium) have a more flexible structure that enables bond rotation.



1. The distance between quaternary groups in the flexible depolarizing agents can vary up to the limit of the maximal bond distance (1.45 nm for decamethonium).
2. They are structurally related to acetylcholine.
3. As with Acetylcholine, the positive nitrogen atoms of NMBDs are attracted to α subunits of the postsynaptic nicotinic receptor.
4. Many NMBDs (e.g. succinylcholine, pancuronium and atracurium) contain two quaternary ammonium cations.
5. These bisquaternary amines are more potent than monoquaternary amines (e.g. ocuronium, tubocurarine and vecuronium), which have only one permanent quaternary cation and one tertiary amine.
6. At physiological pH, and especially in acidotic conditions, the tertiary amine can become protonated and therefore positively charged, increasing the potency of monoquaternary NMBDs. This factor has clinical significance.
7. The two quaternary ammonium groups are separated by a bridging structure that is lipophilic and varies in size. The bridging structure varies with different series of NMBDs and is a major determinant of their potency.

Now we will start our next module

Module 3 MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS (DRUGS)

Normal physiology at neuromuscular junction

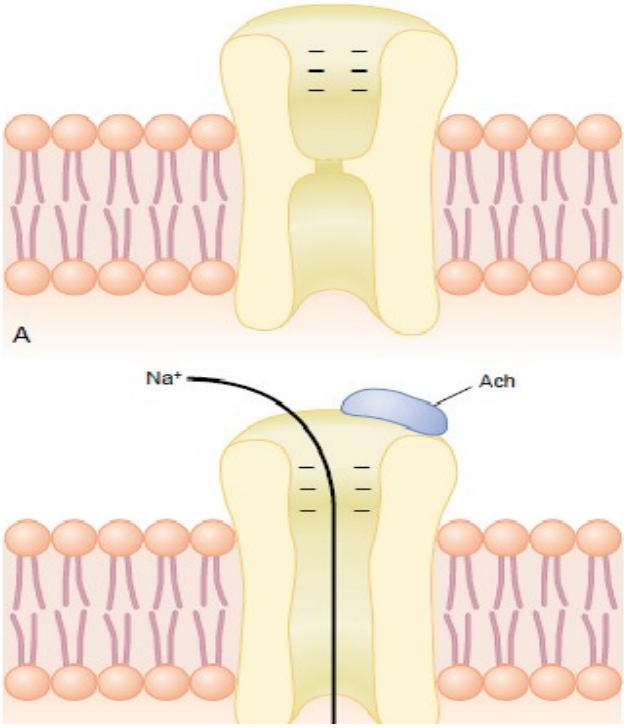


Fig1. Acetylcholine channel. As the acetylcholine (Ach) become attached leads to conformational change thereby causing the opening of channel, allowing sodium ions to enter the muscle fibre and excite contraction.

Acetylcholine activates mainly two types of receptors called muscarinic and nicotinic. Muscarinic receptors are found on all effector cells that are stimulated by the postganglionic cholinergic neurons of either the parasympathetic nervous system or the sympathetic system. Nicotinic receptors are found in the autonomic ganglia at the synapses between the preganglionic and postganglionic neurons of both the sympathetic and parasympathetic systems and the neuromuscular junctions in skeletal muscle. Skeletal muscles are innervated by somatic motor nerves, which originate in the spinal cord, terminate at muscle cells, and release acetylcholine as their neurotransmitter. Upon arrival of an action potential, acetylcholine is released from synaptic vesicles by exocytosis, crosses the synapse, and interacts with skeletal muscle nicotinic cholinergic receptors to depolarize the postsynaptic membrane. When the membrane gains acetylcholine threshold, a muscle action potential is generated and propagates along the fibre to initiate excitation-contraction coupling. Neuromuscular blocking agents interfere with neurotransmission by either:

(1) Competitively antagonizing the actions of acetylcholine at nicotinic receptors, which occur with the nondepolarizing agents.

(2) Occupying and activating the nicotinic receptor for a prolonged period of time, leading to blockade, which occurs with the depolarizing agents.

Drugs can block neuromuscular transmission in three main ways:

1. By inhibiting acetylcholine synthesis- e.g., Hemicholinium and Triehtylcholine
2. By inhibiting acetylcholine release- e.g., Streptomycin, Neomycin and two potent toxins namely Botulinium toxins and β-Bungarotoxins.
3. By interfering with the post synaptic action of acetylcholine.

   This category can be further divided into:

I. Non-depolarizing blocking agents

II. Depolarizing blocking agents

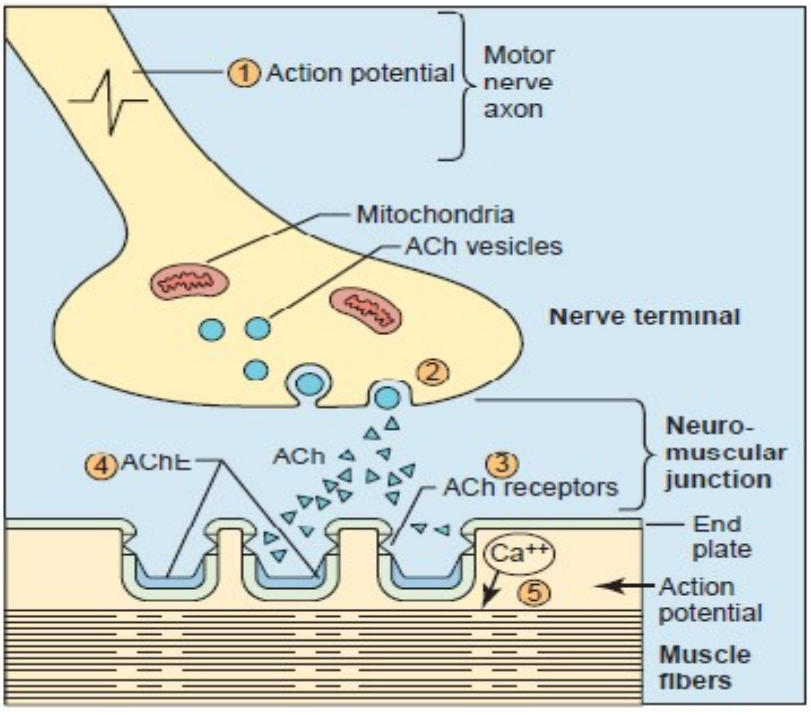


Fig2. Neuromuscular transmission and sites of drug action.

(1) The action potential is conducted down the motor nerve axon and can be blocked by Na+ channel blockers, such as local anesthetics or tetrodotoxin.

(2) When the action potential reaches the nerve terminal, Ca++-mediated vesicular acetylcholine (ACh) release occurs by exocytosis, a process blocked by botulinum toxin or hemicholinium.

(3) After release, ACh diffuses across the synaptic cleft and binds to nicotinic receptors in the motor endplate. The binding can be blocked competitively by nondepolarizing neuromuscular

blockers such as curare or noncompetitively by depolarizing neuromuscular blockers, such as succinylcholine.

(4) ACh is very rapidly hydrolyzed by acetylcholinesterase (AChE), which can be inhibited by cholinesterase inhibitors, such as neostigmine.

(5) ACh-activated nicotinic receptors in the motor endplate generate a muscle action potential, which leads to Ca++ release mediated by ryanodine receptors, initiating excitation-contraction coupling and muscle contraction; this Ca++ release can be blocked by the antispasticity drug dantrolene.

Before proceeding to our next module, I would like to suggest you to kindly visit our website www.cec.nic.in. Here you will find many lectures, e-content, FAQs, LORs, and many more. I hope this website will be a catalyst of learning for you.

So, now we move on to our next module.

Module4

CLASSIFICATION

NMBDs are classified as depolarizing and non-depolarizing drugs according to their action at the postjunctional nicotinic receptor.

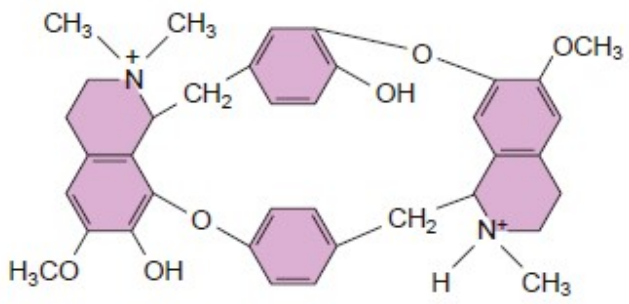
Non-depolarizing (Competitive) Blocking Drugs

Non-depolarizing blocking drugs compete with acetylcholine on the postsynaptic nicotinic receptor. Binding to one or both α-subunits prevents access by acetylcholine to depolarize the receptor so end plate potential becomes very small to initiate the propagated action potential, this results in paralysis of neuromuscular transmition. Non-depolarizing Blocking Drugs do not produce conformational changes in the receptor.

NMBDs can be classified into three classes-

1. **Long acting:** d-Tubocurarine
   Pancuronium
   Doxacurium

Tubocurarine:



d-(+) Tubocurarine

Botanical source of d-tubocurarine is “chondodendron tomentosum” an alkaloid.

Tubocurarine is a lead compound contains isoquinoline, phenol and aromatic ring.

Tubocurarine conatins quaternary nitrogen in two isoquinoline ring which is essential for neuromuscular blocking action.

Tubocurarine is a nondepolarizing blocking agent used for its paralyzing action on voluntary muscle, the site of action being the neuromuscular junction.

Its action is inhibited or reversed by the administration of acetylcholine esterase inhibitors, such as neostigmine or by edrophonium.

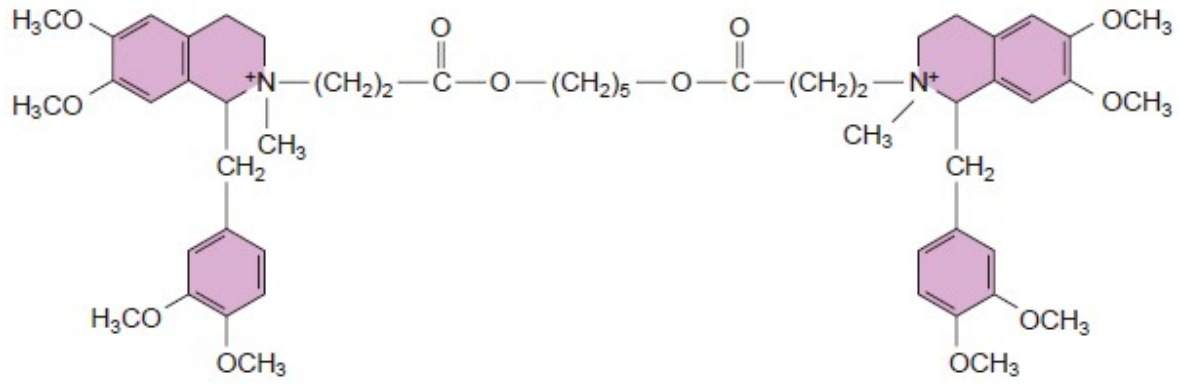
Tubocurarine has a long onset of action and a prolonged duration of effect.

The main side effect of tubocurarine includes histamine release and hypotension, with compensatory acetylcholine tachycardia.

2. **Intermediate acting:** Atracurium

   Vecuronium

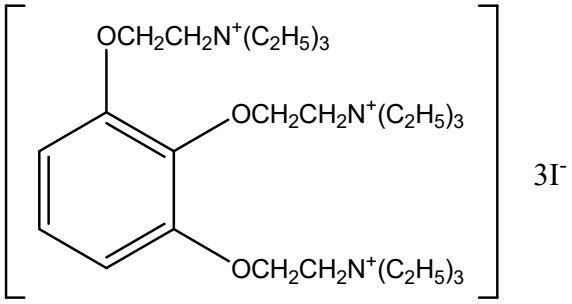
Atracurium:



Atracurium

1. Atracurium is a nondepolarizing neuromuscular blocking agents.
2. It is approximately 2.5 times more potent than d-tubocurarine.
3. Its duration of action (half-life, 0.33 hours) is much shorter than than that of d-tubocurarine.
4. Pharmacologically inactive metabolite is “laudanosine”
5. Atracurium besylate break down by a Hoffman elimination reaction.
6. AcetylcholineE inhibitors antagonize paralysis by atracurium.

Short acting: Gallamine Triethiodide

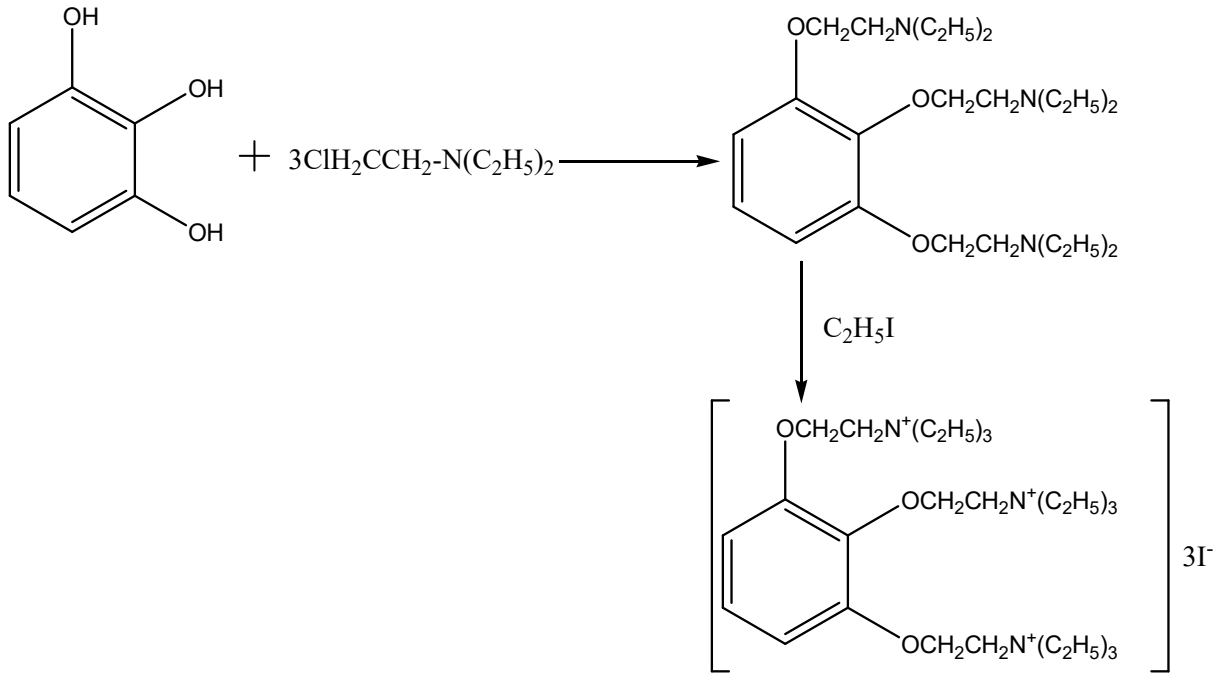


Gallamine Triethiodide

2-(2,3-bis((triethylammonio)methoxy)phenoxy)-*N*,*N*,*N*-triethylethanaminium

Synthesis

Pyrogallol is condensed with 2-chlorotriethylamine and the resultant triamine is quaternized with ethyl iodide in boiling acetone.



Module5 DEPOLARIZING BLOCKING DRUGS

Depolarizing neuromuscular blocker such as succinylcholine produced prolong depolarization of the end plate result in-

1. Desensitization of nicotinic acetylcholine receptor (nAcetylcholineR).
2. Inactivation of voltage-gated sodium channels at the neuromuscular junction.
3. Increases in potassium permeability in the surrounding membrane.

Drugs in the category of depolarizing blocking agents depolarize the membrane of the muscle end plate. They depolarize by opening Na^+ channels depolarization show similar effect like Acetylcholine on ganglia and neuromuscular junctions (i.e., it's so called nicotinic effect). This phenomenon is known as *Acetylcholineyphylaxis*, or *desensitization*.

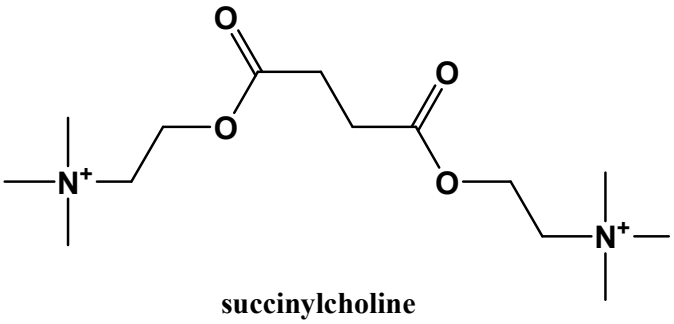
Depolarizing agents produce dual mechanism and blockade occurs in two phases-

***Phase I block*:** This phase is a consequence of prolonged depolarization, rendering the membrane unresponsive to further stimuli. It is characterized by initial muscle fasciculations followed by a flaccid paralysis that is not reversed, but intensified, by administration of AChE inhibitors. .It is rapid in onset, results from persistent depolarization of muscle end plate.

Phase II block: This phase progresses to a state in which the block appears similar to that produced by nondepolarizing agents, that is, it becomes responsive to high concentrations of

ACh and can be reversed by AChE inhibitors. It is slow in onset and results from desensitization of the receptor to acetylcholine.

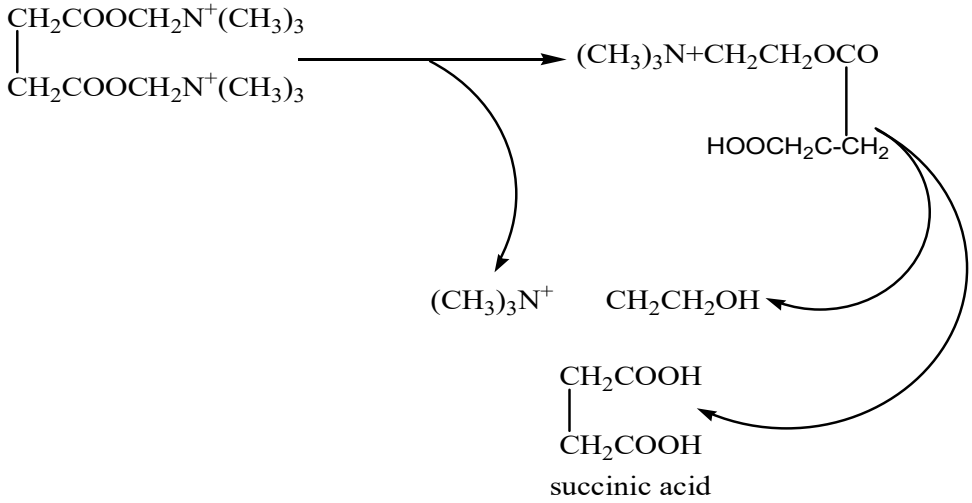
1. Succinylcholine



succinylcholine

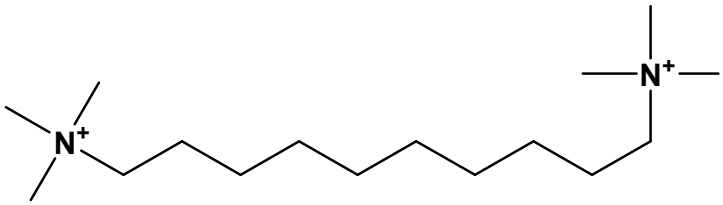
N,*N*,*N*-trimethyl-2-(4-oxo-4-(2-(trimethylammonio)ethoxy)butanoyloxy)ethanaminium

1. Succinylcholine chloride has very short duration of action.
2. It shows quick recovery because of its rapid hydrolysis after injection.
3. Its action with that of d-tubocurarine is not antagonized by AChE enzymes.
4. Succinylcholine act normally for about 3 min., and hydrolyzed by plasma cholinesterase.



Metabolism of Succinylcholine

❖ Decamethonium



Decamethonium

$N^1,N^1,N^1,N^{10},N^{10},N^{10}$-hexamethyldecane-1,10-diaminium

1. Decamethonium has a short duration of action.
2. It is partial agonist of nicotinic receptor.
3. In the process of binding, decamethonium depolarizes the motor endplate, but since the decamethonium itself is not degraded, the membrane remains depolarized and unresponsive to normal acetylcholine release.
4. Decamethonium does not produce unconsciousness and anesthesia.

Friends, as you can see in this table, different antagonizing agents are described along with their mechanism of action , like edrophonium is given in dose of 10 mg and work by inhibiting AChE inhibitor.

Table.1 Antagonism of neuromuscular blocking agents

Antagonizing agents	**Dose**	**Mechanism of action**
Edrophonium	10 mg	Acetylcholinesterase inhibitors
Edrophonium	0.05-0.1 ml/kg	Acetylcholinesterase inhibitors with anticholinergic
Neostigmine	0.5-1.0 mg	Reversible acetylcholinesterase inhibitors
Pyridostigmine	10 mg	Reversible acetylcholinesterase inhibitors

Table.2 Significant drug interaction with neuromuscular blocking agents

S. No.	**Drug/class**	**Clinical effect**
1.	Antiarrhythmic agents (e.g., Quinidine, Procainamide, Lidocaine)	Enhance NMB activity
2.	Antibiotics	Respiratory depression, excessive

	(e.g., aminoglycosides, tetracyclins, polymyxins, clindamycin, pipercillin)	blockade
3.	Antiepileptic (eg., carbamazepine, fosphenytoin, phenytoin)	Rapid recovery time after NMB administration
4.	Calcium- channel blockers (verapamil, nicardipine)	Enhances NMB activity
5.	Inhalation anesthetics	Enhance NMB activity
6.	Oral contraceptives	Prolonged NMB activity
7.	Tricyclic antidepressants	Risk of ventricular arrhythmia

So friends, here I would like to summarize my topic

SUMMARY

Neuromuscular blocking agents block the transmission of acetylcholine at the motor end plate so consider as nicotinic antagonist. Neuromuscular blocking agents are also called skeletal muscles relaxants. The therapeutic use of these compounds is primarily as adjuvants in surgical anesthesia to obtain relaxation of skeletal muscle. The main site of action of **neuromuscular blocking agents** (muscle relaxants) is on the nicotinic cholinergic receptor at the endplate of muscle. They also have effects at presynaptic receptors located on the nerve terminal. The neuromuscular junction consists of the axon imposing onto a specialized area of the muscle known as the muscle end plate.

Structurally, all the NMBDs are available as quaternary ammonium compounds. The type of alkyl carbon (methyl, ethyl) indicates the charge distribution and binding characteristic of onium compounds. NMBDs are classified as depolarizing and non-depolarizing drugs according to their action at the postjunctional nicotinic receptor.

Neuromuscular blocking agents interfere with neurotransmission by either:

(1) Competitively antagonizing the actions of Acetylcholine at nicotinic acetylcholine receptors, which occurs with the nondepolarizing agents.

(2) Occupying and activating the nicotinic receptor for a prolonged period of time, leading to blockade, which occurs with the depolarizing agents.

Thus, an understanding of the pharmacology of **neuromuscular blocking agents** and reversal drugs is essential.

CONCLUSION:

With all these information here we comes to end of today's lecture. Do keep in mind what we discussed today. Time for you to self study. This is Shaila Jain signing off.

LOR:

Q.1. Explain the phase I block in depolarizing neuromuscular agents?

Ans. Phase I is a consequence of prolonged depolarization, rendering the membrane unresponsive to further stimuli. It is characterized by initial muscle fasciculations followed by a flaccid paralysis that is not reversed, but intensified, by administration of AChE inhibitors. .It is rapid in onset, results from persistent depolarization of muscle end plate.

Q.2. Briefly differentiate the depolarizing and nondepolarizing agents?

Ans. The agent which depolarize the membrane of the muscle end plate occupying and activating the nicotinic receptor are called as depolarizing agents, while Non-depolarizing blocking agents compete with acetylcholine on the postsynaptic nicotinic receptor.

Q.3. What is nondepolarizing blocking agents?

Ans. Non-depolarizing blocking agents are those agents which compete with acetylcholine on the postsynaptic nicotinic receptor.

Q.4. Describe the unwanted effects of neuromuscular blocking drugs.

Ans. The unwanted effects are fall in arterial pressure, tachycardia and hypertension, histamine release and pseudo cholinesterase inhibitors activity.

Q.5. Explain the normal physiology at neuromuscular junction.

Ans. Skeletal muscles are innervated by somatic motor nerves, which originate in the spinal cord, end at muscle cells, and release acetylcholine as their neurotransmitter. Upon arrival of an action potential, acetylcholine is released from synaptic vesicles by exocytosis, crosses the synapse, and interacts with skeletal muscle nicotinic cholinergic receptors to depolarize the postsynaptic membrane.

Q.6. Elucidate the structural feature of neuromuscular blocking drugs.

Ans. All the NMBDs available are quaternary ammonium compounds. The type of alkyl carbon (methyl, ethyl) indicates the charge distribution and binding characteristic of onium compounds. Non-depolarizing drugs are generally bulky and more rigid than depolarizing drugs.

As the steric hindrance to receptor increases the potency decreases. l-Tubocurarine is comparatively less potent than d-tubocurarine.

Q.7. What is neuromuscular transmition blocking mechanism?

Ans. Drugs can block neuromuscular transmission in three main ways:

1. By inhibiting acetylcholine synthesis- e.g., Hemicholinium and Triehtylcholine
2. By inhibiting acetylcholine release- e.g., Streptomycin, Neomycin and two potent toxins namely Botulinium toxins and β-Bungarotoxins.
3. By interfering with the post synaptic action of acetylcholine.

Q.8. Explain the salient features of d-tubocurarine?

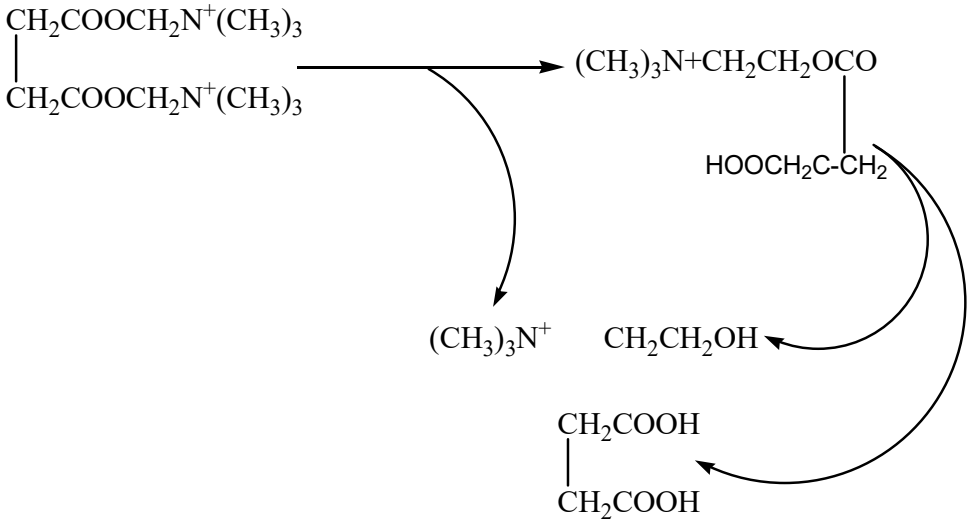
Ans. Botanical source of d-tubocurarine is "chondodendron tomentosum" an alkaloid.

Tubocurarine is a nondepolarizing blocking agent used for its paralyzing action on voluntary muscle, the site of action being the neuromuscular junction.

Its action is inhibited or reversed by the administration of acetylcholine esterese inhibitors, such as neostigmine or by edrophonium.

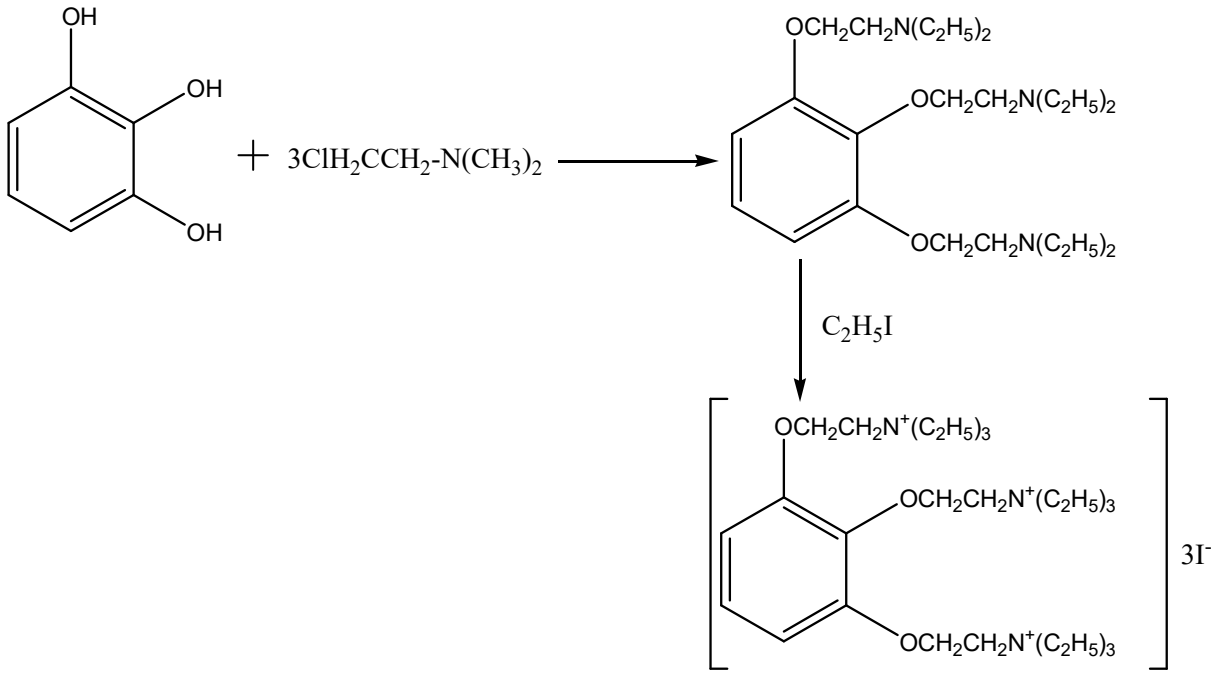
Q.9. Explain the metabolism of succinylcholine.

Ans. The following chemical metabolism reaction showed the metabolism of succinylcholine



Q.10. Explain the synthesis of Gallamine triethiodide.

Ans. The following scheme showed the synthesis of Gallamine triethiodide



FAQs:

Q.1. What is the therapeutic use of neuromuscular blocking agents?

Ans. The therapeutic use of these compounds is primarily as adjuvants in surgical anesthesia to obtain relaxation of skeletal muscle. They also used in various orthopedic procedures, such as alignment of fracture and correction of dislocation.

Q.2.Which stereoisomer of tubocurarine is potent?

Ans. d- tubocurarine is more potent than l-tubocurarine.

Q.3.What do you understand by depolarization?

Ans. Activation of voltage- gated sodium channels at the neuromuscular junction.

Q.4. What is the botanical source of "Tubocurarine"?

Ans. Botanical source of d-tubocurarine is "chondodendron tomentosum" an alkaloid.

Q.5. What is the main structural requirement for NMB action with nicotinic receptor?

Ans. The quaternary ammonium nitrogen and alkyl carbon (methyl, ethyl) determines the charge distribution and binding characteristic as well as the inhibition of neurohumoral transmition at neuromuscular junction.

Q.6. Define skeletal muscle relaxant?

Ans. Neuromuscular and ganglionic blocking agents are called skeletal muscle relaxat.

Q.7. Which mechanism is required for the break down of Atracurium besylate?

Ans. Atracurium besylate is break down by a Hoffman elimination reaction.

Q.8. In which category neuromuscular blocking agents are classified?

Ans. On the basis of mechanism of action neuromuscular blocking agents are classified as

I. Depolarizing blocking agents.

II. Nondepolarizing blocking agents.

Q.9. Which category of drugs antagonise the action of neuromuscular blocking agents?

Ans. Acetylcholinesterase inhibitors with anticholinergic drugs antagonise the action of neuromuscular blocking agents.

Q.10. Which structural unit of nicotinic receptor are responsible for neuromuscular blocking action?

Ans. The α subunit of postsynaptic nicotinic receptor is responsible, acetylcholine, the positive nitrogen atoms of NMBDs are attracted to α subunits and cause neuromuscular blocking action.

MCQs:

Q.1. The duration of action of non-depolarizing neuromuscular blocking drugs may be prolonged by:

a) Phenytoin

b) Carbamazepine

c) Lidocaine

d) pipercillin

Q.2. Tubocurarine is a lead compound for a class of medicinally useful compounds.

a) A neuromuscular blocker

b) A cardiovascular agent

c) An anti-asthmatic drug

d) An analgesic

Q.3. What sort of receptor is the nicotinic receptor?

a) A G- protein coupled receptor

b) A kinase linked receptor

c) An intracellular receptor

d) An ion channel

Q.4. In tubocurarine what structural feature is crucial to its activity?

a) The phenolic ring

b) The Hydrogen bond

c) The two positively charged nitrogen atoms on isoquinoline ring

d) The aromatic ring

Q.5. Atracurium is used intravenously as a neuromuscular blocker. The molecule undergo a chemical degradation at slightly alkaline pH. What is the name of this reaction?

a) Hofmann rearrangement

b) Hofmann elimination

c) Cope rearrangement

d) McLafferty rearrangement

Q.6. Which neuromuscular blocking drugs has short duration of action?

a) d-Tubocurarine

b) Pancuronium

c) Doxacurium

d) Gallamine

Q.7. Calcium- channel blockers

a) Respiratory depression, excessive blockade with NMB

b) Rapid recovery time after NMB administration

c) Enhances NMB activity

d) Risk of ventricular arrhythmia with NMB

Q.8. Which of the following is the neuromuscular blocking agent with the shortest onset of action?

a) Mivacurium

b) Vecuronium

c) Rapacuronium

d) Succinylcholine

Q.9. Which of the following is antagonistic to neuromuscular blocking agents?

a) Neostigmine

b) fosphenytoin

c) Aspirin

d) Quinidine

Q.10. Which of the following is depolarizing neuromuscular blocking agents?

a) Mivacurium

b) Vecuronium

c) Rapacuronium

d) Succinylcholine

Link:

1) **http://www.LWW.com.**
2) **http://www.springer.de**