TOPIC: **NEUROMUSCULAR BLOCKING DRUGS**

What are neuromuscular blocking drugs?

Drugs that cause skeletal muscle relaxation by interrupting the transmission of nerve impulses at the neuromuscular junction

- Neuromuscular blockers have no analgesic or amnestic properties.
- Inappropriate use leads to a state where the patient is paralyzed but not anaesthetized.

What is the purpose of skeletal muscle relaxation?

- To facilitate tracheal intubation
- To facilitate mechanical ventilation
- To optimize surgical working conditions

How skeletal muscle relaxation can be achieved?

- Deep inhalational anesthesia
- Regional anesthesia
- Administration of neuromuscular blocking agents

History of Muscle relaxants

- 1932- dTC was used to control skeletal muscle spasms
- 1942- Griffith & Johnson suggested dTC for skeletal muscle relaxation during surgery
- 1949- Neuromuscular blocking effects of Succinylcholine recognized
- **1952- Sch introduced by Thesleff & Foldes**

  Its use permitted rapid endotracheal intubation
- 1967- Introduction of Pancuronium
- 1980- Introduction of Atracurium & Vecuronium
- 1995- Introduction of CisAtracurium
- 1997- Introduction of Mivacurium & Rocuronium

Classification of neuromuscular blocking agents on the basis of their *mechanism of action:*

- Depolarizing Neuromuscular blockers
- Nondepolarizing Neuromuscular blockers

DEPOLARISING NEUROMUSCULAR BLOCKERS:

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The only depolarizing neuromuscular blocker in use is **SUCCINYLCHOLINE.** Because of its early onset and short duration it is an ideal muscle relaxant for intubation but due to its side effects it should be used only in rapid sequence and difficult airway management.

Succinylcholine physically resembles acetylcholine (two molecules).

Onset of action: - 20 – 30 seconds

Duration of action: - 3 – 5 minutes**.**

Dose:-

- ED_{95} is 0.51-0.63 mg/kg
- Intubating dose 1-1.5mg/kg (*IV*)

0.6mg/kg is adequate

NO SINGLE PERFECT INTUBATING DOSE OF SCH

- Maintenance dose by boluses 0.15 mg/kg
- Maintenance dose by Infusion 2-15 mg/min
- Infants and small children- 2 mg/kg (IV)
- Intramuscular dose- 3-4 mg/kg (max. 150mg total)

Clinical Uses:

- To facilitate tracheal intubation- twice ED_{95}. Especially Emergency and Difficult intubation
- To provide good surgical working conditions- 90% suppression of single twitch response
- Effective treatment of laryngospasm (0.1mg/kg)
- For patients who require mechanical ventilation in critical care
- To reduce intensity of contractions during ECT
- To facilitate Endoscopic procedures
- To facilitate Orthopedic procedures

Veterinary use- Sch used as an euthanasia agent during culling operations of elephants and horses

Contraindications:

- Hyperkalemia- k+>5.5 mEq/L
- Head injury- increases ICT
- New borns and infants.

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- Glaucoma and eye injuries- increases IOP
- Renal failure.
- Metabolic acidosis and shock
- Spinal cord injury.
- Susceptibility to Malignant Hyperthermia
- Tetanus
- Shock
- Guillain barre syndrome

Available forms

- Aqueous solutions
  - Multi dose vials
  - Ampoules
- Crystalline powder- reconstituted with NS or D5

METABOLISM

It is immediately metabolised in **plasma by pseudo cholinesterase** (butyl cholinesterase) which is synthesized by liver so to prevent its metabolism in plasma it should be given at **faster rate.**

MECHANISM OF ACTION:

At neuromuscular junction succinylcholine(Sch) acts like acetylcholine(Ach) attaching to the same site of Ach and producing the action exactly like Acetylcholine.Ach is immediately metabolised by cholinesterase present at neuromuscular junction but succinylcholine metabolism depends on the concentration gradient of Sch between plasma and neuromuscular junction. So excessive availability of Sch at NM junction produces repeated depolarisation and contractions (fasciculation's).

SYSTEMIC EFFECTS:

CVS:

It produces muscarinic effects similar to acetylcholine. Therefore can cause Bradycardia

HYPERKALEMIA: This is due to excessive muscle fasciculation's.

CNS:

SCh increases intracranial tension {due to contraction of neck muscles, blocking venous-outflow (jugular veins) from cranium}

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EYE:

Ocular muscles are multiple innervated muscles which undergo tonic contraction after Succinylcholine increasing the intra ocular tension(IOT)

GIT:

Intragastric pressure is increased due to contraction of abdominal muscles

Increased salivations

Increased gastric secreations

Increased peristalsis.

Non depolarizing muscle relaxants

Classification:

These are broadly divided into:-

Steroidal Compounds	**Benzylisoquinoline compounds**
• Pancuronium	d-Tubocurare
• Vecuronium	Doxacurium
• Pipecuronium	Atracurium
• Rocuronium	Mivacurium
• Rapacuronium	Cis-Atracurium
	Metocurine

(NOTE) The basic difference between steroidal and BZIQ compounds are that histamine release is seen with BZIQ compounds and vagolytic property with steroidal compounds.

On the basis of duration of action NDMR are classified as :

LONG ACTING	**INTERMEDIATE ACTING**	**SHORT ACTING**
D Tubocarae	Vecuronium	Mivacurium
Gallamline	Rocuronium	Rapacuronium
Pancuronium	Atracurium	Gantacurium (shortest acting)
Pipecuronium	Metocurine	

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Doxacurium (longest acting)	Cis - Atracurium	

STEROIDAL COMPOUNDS

VECURONIUM:

- commonly used muscle relaxant
- Dose for intubation :- 0.1 – 0.2 mg/kg
- Drug is unstable in solution hence supplied as lyophilized powder.
- Onset of action :- 2 – 3 minutes
- Duration of action :- 15 – 20 minutes
- It maintains hemodynamic stability
- Hypercarbia after administration of Vecuronium may potentiate drug effect.
- It undergoes both hepatic (30-40%) metabolism and renal excretion (25%)

USES

It is most cardio vascular stable therefore muscle relaxant of choice for cardiac patients

- Intermediate acting muscle relaxant during anaesthesia

ROCURONIUM:

- It is a derivative of Vecuronium with $1/8^{th}$ potency
- It is an intermediate acting drug
- Rapid onset of action (1-2 min.)
- Dose for intubation :- 0.6 – 1 mg/kg
- Non depolarizer of choice for intubation
- Muscle relaxant of choice for precrurazation
- Rocuronium is preferred over Vecuronium for prolonged use in ICU because of inactive metabolites
- Only IM routed non depolarizing agent
- It has mild vagolytic property
- Undergoes no metabolism mainly eliminated through liver ,only 10% by kidney thus safe in renal failure

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PIPECURONIUM:

- It is long acting non depolarizing muscle relaxant
- Dose for intubation :- 0.07 – 0.085 mg/kg IV
- Duration of effect:- 47 – 124 minutes
- No vagolytic activity thus Cvs stable

BENZYLISOQUINOLINE COMPOUNDS

ATRACURIUM:

- Available as Atracurium besylate, stored at 4◦ c
- Acidic compound, precipitates if given in IV line containing alkaline solution like thiopentone
- Dose 0.5 – 0.6 mg/kg
- Onset of action 2 – 3 min.
- Duration of action 10 – 15 min.
- Causes hypotension, bronchospasm because of release of histamine
- At higher doses its metabolic product Laudonosine can cross blood brain barrier and can produce convulsions

METABOLISM OF ATRACURIUM:

- It has unique method of degradation. Its metabolism is independent of hepatic and renal functions. It undergoes spontaneous degradation in plasma called Hoffman degradation

USES:

- **Atracurium** is relaxant of choice in:
  - Hepatic failure
  - Renal failure
  - If reversal agent is contraindicated
  - Myasthenia gravis
  - New born
  - Old age

CIS – ATRACURIUM:

- It is an isomer of Atracurium, 4 times more potent
- Preferred over Atracurium as Does not release histamine and Laudonosine production is 5 times lesser than Atracurium

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- It also undergoes Hoffman's elimination

MIVACURIUM:

- Like Sch. It is metabolized by plasma pseudo cholinesterase
- Onset of action is 2-3 minutes
- Short duration of action 5- 10 minutes therefore muscle relaxant of choice for day care surgery
- Dose of intubation is 0.2 – 0.25 mg/kg
- Releases histamines thus can cause transient hypotension and bronchospasm

DOXACURIUM:

- Duration of action is 60 minutes ,(longest acting non depolarizer)
- Almost completely eliminated unchanged by kidneys
- It is most potent non depolarizing muscle relaxant
- Onset of action is similar to Atracurium

REVERSAL OF NEURO MUSCULAR BLOCK

- Residual neuro muscular block, at the end of the surgical procedure, is reversed with the help of **anticholinestrerases.**

MECHANISM OF ACTION:

- **Anticholinestrerases** inhibit acetyl cholinesterase which is responsible for rapid hydrolysis of Ach at NMJ. As a result concentration of Ach rises at the NMJ.More number of molecules are then available to interact with nicotinic acetylcholine receptors, thereby overcoming the effects of NMBs

NEOSTIGMINE:

- Poorly lipid soluble
- Quaternary ammonium compound
- Onset of action: 7-11 min
- 50% of the injected dose is eliminated through kidneys
- In the absence of renal function , the drug is metabolised in liver
- Elimination half life:- 60-120 min

SYSTEMIC EFFECTS OF NEOSTIGMINE:

- Bradycardia, bradyarrhythmias and sinus arrest may be caused. This is prevented by prior administration of Anticholinergic drug
- Increased secretions from salivary,bronchial,lacrimal ,sweat and gastric glands

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- Motility of gastrointestinal tract is increased
- Cholinergic crisis may occur in patients suffering from myasthenia gravis

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