NEUROMUSCULAR BLOCKING AGENTS
&
SKELETAL MUSCLE RELAXANTS (PERIPHERAL)

Prepared By

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- The neuromuscular blocking agents are used primarily in conjunction with general anaesthetics to provide muscle relaxation for surgery.

- Skeletal muscle relaxants are drugs that act peripherally at neuromuscular junction/muscle fibre itself or centrally in the cerebrospinal axis to reduce muscle tone and/or cause paralysis.

CLASSIFICATION

- **PERIPHERALLY ACTING MUSCLE RELAXANTS**
- **I. Neuromuscular blocking agents**
  - ***A. Non-depolarizing (Competitive) blockers***

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

    2. *Intermediate acting:* *Vecuronium,* Atracurium, Cisatracurium, Rocuronium, Rapacuronium

    3. *Short acting**: Mivacurium***
  - ***B. Depolarizing blockers***
    - Succinylcholine (SCh., Suxamethonium)
    - Decamethonium (C-10)
- **II. Directly acting agents**
  - Dantrolene sodium
  - Quinine

NEUROMUSCULAR BLOCKING AGENTS

- **CURARE:**
- It is the generic name for certain plant extracts used by south American tribals as arrow poison for game hunting.
- The animals got paralysed even if not killed by the arrow.
- Natural sources of curare are *Strychnos toxifera, Chondrodendron tomentosum and related plants.*
- *Muscle paralysing* active principles of these are tubocurarine, toxiferins, etc.
- Tubocurarine was first clinically used in 1930s; many synthetic compounds including *Succinylcholine were* introduced subsequently.
- The latest additions are *doxacurium, pipecuronium, rocuronium, mivacurium, rapacuronium and cisatracurium.*
- **MECHANISM OF ACTION**
- The site of action of both competitive and depolarizing blockers is the end plate of skeletal muscle fibres.

Competitive block (Nondepolarizing block)

- This is produced by curare and related drugs.
- Claude Bernard (1856) precisely localized the site of action of curare to be the neuromuscular junction.
- The competitive blockers have affinity for the nicotinic (N_M) cholinergic receptors at the muscle end plate, but have no intrinsic activity.
- The N_M receptor has been isolated and studied in detail.
- It is a protein with 5 subunits (α2, β, ε or γ and δ) which are arranged like a rosette surrounding the Na+ channel.
- *The* two α subunits carry two ACh binding sites; these have negatively charged groups which combine with the cationic head of ACh → opening of Na+ channel.

Depolarizing block:

- **Decamethonium and Succinylcholine** have affinity as well as submaximal intrinsic activity at the N_M cholinoceptors.
- They depolarize muscle end plates by opening Na+ channels and initially produce twitching.
- These drugs do not dissociate rapidly from the receptor and are not hydrolysed by AChE.
- They induce prolonged partial depolarization of the region around muscle end plate → Na+ channels get inactivated (because transmembrane potential drops to about –50 mV) → ACh released from motor nerve endings is unable to generate action potential → flaccid paralysis.
- A zone of inexcitability is created around the end plate preventing activation of the muscle fibre.
- Depolarizing blockers also have 2 quaternary N+ atoms, but the molecule is long, slender and flexible.

- ***PHASE I BLOCK:***
- *It is rapid in onset, results from* persistent depolarization of muscle end plate and has features of classical depolarization blockade.
- This depolarization declines shortly afterwards and repolarization occurs gradually despite continued presence of the drug at the receptor, but neuromuscular transmission is not restored and phase II block supervenes.
- ***PHASE II BLOCK:***
- *It is slow in onset and results* from desensitization of the receptor to ACh.
- It, therefore, superficially resembles block produced by d-TC.
- The muscle membrane is nearly repolarized, recovery is slow and the block is partially reversed by anti-cholinesterases.
- In man, normally only phase I block is seen.
- Phase II block may be seen when Succinylcholine is injected in high dose or infused continuously.

ACTIONS

Skeletal muscles:

- I.V injection of non-depolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis.
- Fingers are affected first; paralysis spreads to hands, feet—arm, leg, neck, face—trunk—intercostal muscles—finally diaphragm: respiration stops.
- Recovery occurs in the reverse sequence.

Autonomic ganglia:

- Because the cholinergic receptors in autonomic ganglia are nicotinic, competitive neuromuscular blockers produce some degree of ganglionic blockade.
- d-TC has the maximum propensity in this regard, while the newer drugs (vecuronium, etc.) are practically devoid of it.
- Succinyl choline may cause ganglionic stimulation by its agonistic action on nicotinic receptors.

G.I.T:

- The ganglion blocking activity of competitive blockers may enhance postoperative paralytic ileus after abdominal operations.

ACTIONS

C.N.S:

- All neuromuscular blockers are quaternary compounds—do not cross blood-brain barrier.
- Thus, on i.v. administration no central effects follow.
- However, d-TC applied to brain cortex or injected in the cerebral ventricles produces strychnine like effects.

Histamine release:

- d-TC releases histamine from mast cells.
- This does not involve immune system and is due to the bulky cationic nature of the molecule.
- Hypotension occurs.
- Flushing, bronchospasm and increased respiratory secretions are other effects.

ACTIONS

C.V.S:

- d-Tubocurarine produces significant fall in BP.
- This is due to—
  - (a) ganglionic blockade
  - (b) histamine release and
  - (c) reduced venous return
- A result of paralysis of limb and respiratory muscles.
- Heart rate may increase due to vagal ganglionic blockade
- Pancuronium and vecuronium also tend to cause tachycardia.
- All newer non-depolarizing drugs have negligible effects on BP and HR.
- Prolonged administration of succinyl choline has caused cardiac arrhythmias.

PHARMACOKINETICS

- All neuromuscular blockers are polar quaternary compounds—not absorbed orally, do not cross cell membranes, have low volumes of distribution; do not penetrate placental or BBB.
- They are practically always given i.v., though i.m. administration is possible.
- Muscles with higher blood flow receive more drug and are affected earlier.
- The duration of action of competitive blockers is directly dependent on the elimination t½.
- Drugs that are primarily metabolized in the plasma/liver, e.g. vecuronium, atracurium, cisatracurium, rocuronium, and especially mivacurium have relatively shorter t½ and duration of action (20–40 min).
- While those largely excreted by the kidney, e.g. pancuronium, d-TC, doxacurium and pipecuronium have longer t½ and duration of action (>60 min).
- With repeated administration, redistribution sites are filled up and duration of action is prolonged.
- The unchanged drug is excreted in urine as well as in bile.
- Succinylcholine is rapidly hydrolysed by plasma pseudocholinesterase to succinylmonocholine and then to succinic acid + choline (action lasts 5–8 min).

d-Tubocurarine:

- Because of its prominent histamine releasing, ganglion blocking, cardiovascular actions and long duration of paralysis, d-TC is not used now.

Succinylcholine: (50 mg/ml inj)

- It is the most commonly used muscle relaxant for passing tracheal tube.

ADR:

- Muscle fasciculations and soreness, changes in BP and HR, arrhythmias and hyperkalaemia.
- It induces rapid, complete and predictable paralysis with spontaneous recovery in ~5 min.
- Excellent intubating condition *viz.* relaxed jaw, vocal cords apart and immobile with no diaphragmatic movements, is obtained within 1–1.5 min.
- Occasionally SCh is used by continuous i.v. infusion for producing controlled muscle relaxation of longer duration.
- It should be avoided in younger children unless absolutely necessary, because risk of hyperkalaemia and cardiac arrhythmia is higher.
- Risk of regurgitation and aspiration of gastric contents is increased by SCh in GERD patients and in the obese, especially if stomach is full.

Pancuronium:

- A synthetic steroidal compound, ~5 times more potent and longer acting than d-TC.
- Provides good cardiovascular stability (little ganglionic blockade), seldom induces flushing, bronchospasm or cardiac arrhythmias because of lower histamine releasing potential.
- Rapid i.v. injection may cause rise in BP and tachycardia occurs due to vagal blockade and NA release.
- It is primarily eliminated by renal excretion.
- Because of longer duration of action, needing reversal, its use is now restricted to prolonged operations, especially neurosurgery.
- 2 mg/ml in 2 ml amp.

Vecuronium: (4 mg amp, dissolve in 1 ml solvent)

- A close congener of pancuronium with a shorter duration of action due to rapid distribution and metabolism.
- It is excreted mainly in bile, recovery is generally spontaneous, but may need neostigmine reversal.
- Cardiovascular stability is still better due to lack of histamine releasing and ganglionic action.
- Tachycardia sometimes occurs.
- Currently, it is the most commonly used muscle relaxant for routine surgery and in intensive care units.

Atracurium: (10 mg/ml inj in 2 ml vial)

- A bisquaternary competitive blocker, 4 times less potent than pancuronium and shorter acting: reversal is mostly not required.
- The unique feature of atracurium is inactivation in plasma by spontaneous non-enzymatic degradation in addition to that by cholinesterases.
- Its duration of action is not altered in patients with hepatic/renal insufficiency or hypodynamic circulation. Hypotension may occur.
- It is preferred muscle relaxant for liver/kidney disease patients as well as for neonates and the elderly.

Mivacurium:

- It is the shortest acting competitive blocker; does not need reversal.
- Dose and speed of injection related transient cutaneous flushing can occur due to histamine release.
- Fall in BP is possible, but change in HR is minimal.
- It is metabolized rapidly by plasma cholinesterases.
- Prolonged paralysis can occur in pseudocholinesterase deficiency, but this can be reversed by neostigmine.

DRUG INTERACTIONS

- Thiopentone sodium and succinlycholine should not be mixed.
- Genreal anaesthetics increases the action of competitive blockers.
- Calcium channel blockers increases actions.
- Diuretic usage increases hypokalemia.
- Anti-cholinesterases reverses the action of competitive blockers.
- Diazepam and propranolol increases competitive blockade.

USES:

- Used as adjuvant to general anaesthetics.
- Convulsions and trauma from anticonvulsant therapy can be avoided.
- Severe cases of tetanus and status epilepticus, who are not controlled by diazepam or other drugs may be controlled by neuromuscular blockers.
- Critically ill patients in ICU are given with sub-anaesthetic doses of competitive blockers which helps in assisted ventilation.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene Sodium:

- It is chemically and pharmacologically entirely different from neuromuscular blockers.
- Its effect superficially resembles that of centrally acting muscle relaxants.
- Neuromuscular transmission is not affected, but muscle contraction is uncoupled from depolarization of the membrane.
- Dantrolene acts on the RyR1 (Ryanodine Receptor) calcium channels in the sarcoplasmic reticulum of skeletal muscles and prevents Ca2+ induced Ca2+ release through these channels.
- Intracellular release of Ca2+ needed for excitation-contraction coupling is interfered.
- Fast contracting ‘twitch’ muscles are affected more than slow contracting ‘antigravity’ muscles.

Pharmacokinetics:

- Dantrolene is slowly but adequately absorbed from the g.i.t.
- It penetrates brain and produces some sedation, but has no selective effect on polysynaptic reflexes responsible for spasticity.
- It is metabolized in liver and excreted by kidney with a t½ of 8–12 hours.
- Used orally dantrolene (25–100 mg QID) reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis.
- Used i.v. (1 mg/kg repeated as required) it is the drug of choice for malignant hyperthermia.

Adverse effects:

- *Muscular weakness is the* dose limiting side effect.
- Sedation, malaise, light headedness and other central effects occur, but are less pronounced than with centrally acting muscle relaxants.
- Troublesome diarrhoea is another problem.
- Long term use causes dose dependent serious liver toxicity in 0.1–0.5% patients.
- This has restricted its use in chronic disorders.

Quinine:

- It increases refractory period and decreases excitability of motor end plates.
- Thus, responses to repetitive nerve stimulation are reduced.
- It decreases muscle tone in myotonia congenita.
- Taken at bed time (200–300 mg) it may abolish nocturnal leg cramps in some patients.