Neuromuscular Blocking Agents

By Saef B alabbadi
Objectives

- Different in brief between depolarizing and non depolarizing muscle relaxants....

- Depolarizing muscle relaxants:
  - structure and mechanism of action
  - dose, onset and duration of action
  - indications and contraindications
  - side effects
  - factors affecting duration
**Depolarizing muscle relaxants** act as acetylcholine (ACh) receptor agonists as the muscle relaxant continues to bind to the ACh receptor, the end plate cannot repolarize, resulting in a block.

**Non-depolarizing muscle relaxants** function as competitive antagonists. They bind to the ACh receptors but are unable to induce ion channel openings. They prevent ACh from binding and thus end plate potentials do not develop.
Depolarizing muscle relaxants..

* Succinylcholine *

Or Suxamethonium

Sold under trade names: Anectine, Quelicine, Scoline

What's special??
Rapid onset & Short duration

- cause **short-term paralysis** as part of general anesthesia.

- it is perennially popular in **emergency medicine** because it has the **fastest onset and shortest duration** of action of all muscle relaxants.

- Suxamethonium is quickly degraded by plasma **butyrylcholinesterase** and the duration of effect is usually in **the range of a few minutes**
Physical Structure:

consists of two joined Ach molecules:
**Mechanism of action:**

Depolarizing muscle relaxants very closely resemble ACh and readily bind to ACh receptors, generating a muscle action potential.

Unlike ACh, however, these drugs are not metabolized by acetylcholinesterase, and their concentration in the synaptic cleft does not fall as rapidly, resulting in a prolonged depolarization of the muscle end-plate.

Continuous end-plate depolarization causes muscle relaxation because opening of perijunctional sodium channels is time limited (sodium channels rapidly “inactivate” with continuing depolarization (fasciculation))......> flaccid paralysis
After the initial excitation and opening these sodium channels inactivate and cannot reopen until the end-plate repolarizes.

The end-plate cannot repolarize as long as the depolarizing muscle relaxant continues to bind to Ach receptors. this is called a phase I block.

More prolonged end-plate depolarization can cause poorly understood changes in the ACh receptor that result in a phase II block, which clinically resembles that of nondepolarizing muscle relaxants. Desensitization (unresponsiveness) then muscle exhaustion & paralysis
Drug remains binding to Ach receptors causing desensitization till it diffuse away from end plate to plasma.

Because succinylcholine is not metabolized by acetylcholinesterase, it unbinds the receptor and diffuses away from the neuromuscular junction to be hydrolyzed in the plasma and liver by another enzyme, pseudocholinesterase.

- pseudocholinesterase = Butyrylcholinesterase
depolarization caused by Succinylcholine mimicking the effect of acetylcholine but without being rapidly hydrolysed by acetylcholinesterase. This depolarization leads to desensitization.

The muscle became exhausted so no depolarization occurs.
Succinylcholine remains popular due to its rapid onset of action (30–60 s) short duration of action (typically less than 10 min), can be prolonged by high doses, infusion of Succinylcholine, or abnormal metabolism (hypothermia, pregnancy), liver disease, kidney failure.

Short duration of action due to metabolization of Succinylcholine by pseudocholesterase into Succinylmonocholine.

Side effect of the drug: malignant hyperthermia, arrythmia and hyperkalemia. Cardiac arrest so this reduce its use.

What's problem?? There is no antagonists drug for succinylcholine, we just observe the patient in ICU.
Prolonged paralysis from succinylcholine caused by abnormal pseudocholinesterase (atypical cholinesterase) should be treated with:
-- continued mechanical ventilation and sedation until muscle function returns to normal by clinical signs

For adult dose of Succinylcholine for intubation is>> 1 to 1.5 mg/kg IV
Pharmacokinetics:

Administered intravenously (IV)

Due to rapid inactivation by plasma cholinesterase, given by continued infusion
Sequence of paralysis:

short muscles are paralyzed first then later occurs paralysis of other muscles.

.Finger and orbit muscles → Limbs and trunk muscles
   Neck muscles → Intercostals → DIAPHRAGM

Recovery from paralysis occurs in reverse sequence!
So recovery start from diaphragm ,,don’t fear 😊
Indications:

*our key: rapid onset, short duration*

1– Non Fasting Patients: i.e. Emergency, cesarean section
   Rapid sequence intubation (RSI)

2– predicted difficult intubation (cuz it’s rapid onset and short duration)

3– prior to Electroconvulsive shock therapy (ECT): why ??
   I need the patient for just 1 min so succinylcholine useful here

4– Operations of short duration where muscle relaxation is needed.
   (For correction of dislocation and alignment of fractures)

5– For laryngoscopy, bronchoscopy, esophagoscopy
Clinical Contra-indecations...

1– known allergy / hypersensetivity

2– positive Hx of malignant hyperthermia

3– routine management of children

4– myotonia (M. congenita, M.dystrophica, paramyotonia congenita) for all muscle relaxant

5– patient have risk of a hyperkalemic response to succinylcolin

.examples
Conditions causing susceptibility to Succinylcholine induced hyperkalemia.....

- Burn injury
- Massive trauma
- Severe intra abdominal infection
- Spinal cord injury
  - Encephalitis
  - Stroke
- Severe Parkinson disease
- Tetanus
- Prolonged total body immobilization
  - Polyneuropathy
  - Closed head injury
- Hemorrhagic shock with metabolic acidosis
- Myopathies (eg, Duchenne dystrophy)
Side effects:

- **Cardiac**: Bradycardia (children & second bolus) / Dysarrythmia / nodal bradycardia / ventricular ectopy / Sinus arrest

  *On* higher doses usually increase heart rate and contractility and elevate circulating catecholamine levels.

Intravenous **atropine** (0.02 mg/kg in children, 0.4 mg in adults) is normally given prophylactically.

- **Fasciculation**: visible motor unit contraction, prevented by pretreatment with a small dose of nondepolarizing relaxant

- **Hyperkalemia**
- **Muscle Pains** - postoperative myalgia (prevented by rocuronium and NSAIDs prior it) / myoglobinemia / increases in serum creatine kinase / myoglobinurea

- **Intragastric Pressure Elevation**

- **Intraocular Pressure Elevation** prevented by pretreatment with a nondepolarizing agent (not always)

- **Masseter Muscle Rigidity** can be sign of malignant hyperthermia

- **Malignant Hyperthermia**

- **Generalized Contractions**

- **Prolonged Paralysis**

- **Intracranial Pressure** It can also be prevented by pretreating with a nondepolarizing muscle relaxant and administering intravenous lidocaine (1.5–2.0 mg/kg) 2 to 3 min prior to intubation

- **Histamine Release**