Neuromuscular Blocking Agents

By

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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 a block.

whereas non_depolarizing muscle relaxants function as competitive antagonist they bind to the ACh receptors but unable to induce ion channel openings. They prevent ACh from binding and thus end plate potentials do not develop.
Depolarizing muscle relaxants..

*Succinylcholine*
Other name: Suxamethonium

*The only depolarizing muscle relaxant in clinical use today.
*Sold under trade names: Anectine, Quelicine, Scoline.
**Succinylcholine**

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

- In plasma it undergo spontaneous hydrolysis by endogenous plasma cholinesterase (**pseudochocholienesterase**)  
- **pseudochocholienestrase** == **Butyrylcholinesterase**
Metabolism & Excretion:

Succinylcholine remains popular due to its rapid onset of action (30–60 s) and short duration of action (typically less than 10 min), can be prolonged by high doses, infusion of Succinylcholine, or abnormal metabolism (hypothermia, reduced pseudocholienesterase level which decrease in pregnancy (2–3 min reduction), liver disease, kidney failure, and certain drug therapies).

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

The usual adult dose of Succinylcholine for intubation is 1 to 1.5 mg/kg IV.

Repeated small boluses (5–10 mg) or a Succinylcholine drip (1 g in 500 or 1000 mL, titrated to effect) can be used during surgical procedures that require brief but intense paralysis (e.g., otolaryngological endoscopies).

The availability of intermediate acting nondepolarizing muscle relaxants has reduced the popularity of Succinylcholine infusions.
• dosage requirements for pediatric patients are often greater than for adults.
• Succinylcholine should be stored under refrigeration (2–8°C), and should generally be used within 14 days after removal from refrigeration and exposure to room temperature.
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 which may lead to death

.Finger and orbit muscles $\rightarrow$ Limbs and trunk muscles $\rightarrow$ Neck muscles $\rightarrow$ Intercostals $\rightarrow$ DIAPHRAGM

Recovery from paralysis occurs in reverse sequence!
Indications:

1- Non Fasting Patients: i.e. Emergency, cesarean section, (full stomach)

   Rapid sequence intubation (RSI)

2- predicted difficult intubation

3- prior to Electroconvulsive shock therapy (ECT)

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-indications…

1- inability to maintain airways
2- known allergy / hypersensetivity
3- positive Hx of malignant hyperthermia
4- routine management of children
5- myotonia (M. congenita, M.dystrophica, paramyotonia congenita),
6- patient have risk of a hyperkalemic response to succinylcolin .examples
7- lack of resuscitative equipment
induced susceptibility to Succinylcholine hyperkalemia.

- Burn injury
- Massive trauma
- Severe intra abdominal infection
- Spinal cord injury
- Encephalitis
- Stroke
- Guillain–Barré syndrome
- Severe Parkinson disease
- Tetanus
- Prolonged total body immobilization
- Ruptured cerebral aneurysm
- 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, signaled the paralysis by succenylcholine, 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**
Thank you