THE NORTHERN HOSPITAL

SUXAMETHONIUM

"Gaius Julius Caesar", marble, c.1696, Nicolas Coustou, Louvre Museum, Paris.

...Then catching up with his cohorts at the river Rubicon, the point at which his province ended, he paused for a moment, and contemplating the immensity of what he was about to do, he turned and spoke to his men who were near him. "Even now we could turn back; but once we cross over that small bridge, then there is no turning back, everything will depend on our force of arms…so the die is cast".

Suetonius, "The Twelve Caesars", c 120 A.D

Ever since Caesar's astonishing exploits in his military campaigns of 58-51 BCE, where he conquered the whole of Gaul, routed a Germanic invasion in the far North, and even reached the very ends of the Earth, by reconnoitring the mysterious and fabulous Isle of the Britons, a shadow had been caste over Pompey's achievements that had resulted in an icy coolness between the two. The Senate had become alarmed at the adulation that Caesar had gained, not only from his devoted troops but also the people of Rome. The Senate confidant that they could control Pompey decided to use him, reminding him that he was the heir of Sulla, the First Man in Rome and protector of the senate. He would need to keep the upstart Caesar in close check.

But Caesar now considered himself to be the "First Man" in Rome and a clash with Pompey became inevitable. Julius Caesar had changed the whole "modus operandi" of a Roman army - previously under the Republic the allegiance of the troops was to the Senate - but after many years of bloody war and glorious victories this had changed forever - the loyalty of the troops would no longer lie with the Senate - but with their own commanding general - loyalty had become personal. Caesar decided to confront Pompey and the Senate, but this would mean leading his troops into Italy itself. Roman law specified that only elected consuls could hold imperium within Italy. Any general who entered Italy at the head of armed troops who was not a consul immediately forfeited his imperium over those troops and was therefore no longer legally allowed to command them. He would immediately be declared an outlaw and enemy of the state.

The Rubicon River marked the boundary between the Province of Cisalpine Gaul, which was Caesar's jurisdiction and that of Italy. He took his elite and battle hardened 13th Legion Gemina, to the very river edge itself - before hesitating for one of the few times in his life. He declared to his closest advisors,"Even now we could turn back; but once we cross over that small bridge, then there is no turning back, everything will depend on our force of arms". After some moments of deep reflection he suddenly gave the order to cross the Rubicon - his troops instantly following his fateful command. Suetonius reported that after he had made his decision he muttered to himself the famous line... "so the die is cast". He would defeat Pompey at Pharsalus in 48 BCE - from that moment on the Republic was doomed. His nephew Augustus would become the first Emperor of Imperial Rome.

When we decide to administer the drug suxamethonium, we need be mindful that we have reached our own "Rubicon"- from this point onwards there will be no turning back - the die will have been cast and we are irrevocably committed to the definitive management of the patient's airway.

SUXAMETHONIUM

Introduction

Suxamethonium, (also known as Succinyl Choline), is a fast onset, short acting depolarizing muscle relaxant used to facilitate tracheal intubation.

As for any skeletal muscle relaxation agent suxamethonium should only be used in association with full resuscitation and intubation equipment on hand and only by doctors experienced in managing intubation and anesthetized patients.

Unlike the non-depolarizing neuromuscular blocking drugs suxamethonium has no specific "antidote"

History

Suxamethonium was introduced to clinical practice in 1951. [5]

Chemistry

Suxamethonium is essentially two acetylcholine molecules bound together.

Physiology

There are two types of cholinesterase enzymes in the body:

Acetylcholinesterase, (AChE):

- Also known as RBC cholinesterase, erythrocyte cholinesterase, or (most formally) acetylcholine acetylhydrolase
- It is found primarily in the blood on red blood cell membranes, in neuromuscular junctions, and in neural synapses.

Pseudocholinesterase, (BChE or BuChE):

- Also known as **plasma cholinesterase**, butyrylcholinesterase, or (most formally) acylcholine acylhydrolase,
- It is found in the liver and in plasma.

The difference between the two types of cholinesterase has to do with their respective preferences for substrates: the former hydrolyses acetylcholine more quickly; the latter hydrolyses butyrylcholine more quickly.

An absence or mutation of the pseudocholinesterase enzyme leads to the condition known as pseudocholinesterase deficiency.

This is a silent condition that manifests itself only when people that have the deficiency receive the muscle relaxant suxamethonium.

Classification

The skeletal muscle relaxing agents are broadly divided into two groups:

1. The depolarizing neuromuscular blockers:
    - **Suxamethonium** (or succinyl choline) (short acting)
2. The non-depolarizing neuromuscular blockers:
    - **The aminosteroids**:
        - ♥ Vecuronium (intermediate acting)
        - ♥ Rocuronium (intermediate acting)
        - ♥ Pancuronium (long acting)
    - **Benzyl-iso-quino-liniums**:
        - ♥ Atracurium (intermediate acting)
        - ♥ Cisatracurium (intermediate acting)
        - ♥ Mivacurium (intermediate acting)

Preparation

Ampoules:

- Suxamethonium **100mg / 2ml.**

  Suxamethonium in solution hydrolyses and loses its potency unless refrigerated.

Mechanism of Action

Suxamethonium is a nicotinic acetylcholine receptor **agonist.**

It combines with the cholinergic receptors of the motor end plate to produce polarisation, (which gives rise clinically to skeletal muscle fasciculations).

The end plate then *remains* permeable to sodium and potassium until the drug is removed from the end plate, (predominantly by diffusion back into the plasma) so that further nerve stimuli are totally ineffective.

Suxamethonium has no direct action on smooth muscle structures.

Inhibition of action:

Non-depolarizing muscle relaxant drugs given *prior* to suxamethonium will delay the onset of paralysis caused by suxamethonium.

Enhancement of action:

Cholinergic agents (including neostigmine) will prolong the action of suxamethonium.

The activity of plasma cholinesterase can be reduced by drugs and poisons such as **organophosphates** and **carbamates**, and hence the action of suxamethonium may be greatly enhanced/ prolonged.

The duration of action is prolonged in patients with low plasma pseudocholinesterase levels.

Pharmacodynamics

1. Initial fibrillary skeletal muscle tremors:

    - Fibrillary skeletal muscle tremors are commonly seen after suxamethonium
    - They are due to direct stimulation of the motor nerve ending, with antidromic impulses producing local axon reflexes, hence stimulating other muscle fibers that are supplied by the same nerve fiber.
    - They do **not** appear to be related to the phenomenon of suxamethonium myalgias.
    - They can be reduced by the prior administration of a small (1/10) dose of the usual intubating dose of a non-depolarizing muscle relaxant.
    - These fasciculations are painful to a conscious patient.

2. Skeletal muscle paralysis:

    - Complete skeletal muscle relaxation, (i.e flaccid paralysis) follows the brief initial fibrillary stage.
    - Paralysis will last around 5 - 10 minutes following IV administration.

3. Suxamethonium has no central CNS effects:

- This is critical to appreciate - as paralyzed patients retain full conscious awareness. **Suxamethonium has no sedative or analgesic effects, and should only be used in association with adequate anaesthesia.**

- It is for this reason that an IV anesthetic induction agent is always given prior to the administration of suxamethonium.

Pharmacokinetics

Absorption:

- **Suxamethonium is given by IV rapid bolus injection.**

  - ♥ After IV administration, the onset of action occurs in **30 - 60 seconds** and lasts for **5 - 10 minutes**. Onset times however may be slowed by states of **poor perfusion.**

- It is effective by the IM route as well, though IV is the preferred route of administration.

  - ♥ After IM injection (rarely indicated), onset usually occurs in 3 minutes and lasts 10 - 30 minutes; larger doses produce more prolonged muscle relaxation.

Distribution:

- Suxamethonium is distributed throughout the blood stream, to act on all skeletal muscle.

Metabolism and excretion:

- About 90 % of IV injected suxamethonium is destroyed in the blood before it reaches its site of action. This destruction is by pseudo-cholinesterase as follows:

  Suxamethonium → succinyl-monocholine + choline.

Patients with significantly impaired renal function may occasionally experience prolonged apnoea due to accumulation of succinylmonocholine, (which has some mild effects). [3]

The fraction that does reach the NMJ will have its action terminated by simple diffusion away down a concentration gradient, as there is little pseudo-cholinesterase to hydrolyse it at the NMJ.

About 2 % of the dose is directly excreted by the kidneys.

A small number of people lack plasma pseudo-cholinesterase or have abnormal plasma pseudo-cholinesterase.

In these patients the action of suxamethonium is greatly prolonged, (1-2 hours) and muscle paralysis will continue until the drug is eliminated by other means, (predominantly by renal excretion).

Indications

1. Complete skeletal muscle relaxation for the facilitation of intubation.

2. Suxamethonium is the preferred muscle relaxant for all rapid sequence inductions, (unless there is an absolute contraindication to its use).

Contra-indications/precautions:

1. **As for any skeletal muscle relaxation agent suxamethonium should only be used in association with full resuscitation and intubation equipment on hand and only by doctors experienced in managing intubation and anesthetized patients.**

2. Patients with known significant hyperkalemia:

   Caution is also required in patients who *may have* hyperkalemia from:

   - Major burns (at about 7-10 days)
   - Major crush injuries.
   - Massive digitalis toxicity.

3. Muscular dystrophies:

   - Suxamethonium is generally contraindicated in muscular dystrophies/ congenital myopathies (especially if associated with elevated creatine phosphokinase (CPK) values) or neurological disease involving **extensive muscle wasting** where acute rhabdomyolysis with hyperkalemia can be precipitated.

4. Myasthenia gravis:

   - People with myasthenia gravis respond unpredictably to suxamethonium, and can develop dual (phase II) block; avoid if possible.

5. Personal or family history of **malignant hyperthermia**

6. Low or abnormal plasma cholinesterase

Pregnancy

Safe to use; Australian Category A drug.

Suxamethonium does crosses the placenta, but generally only in very small amounts. Residual neuromuscular blockade may occasionally occur in the neonate after **repeated high doses** of suxamethonium to the mother during delivery by caesarean section. [3]

Adverse Effects

Apart from respiratory arrest, a desired effect, from the point of view of intubation, which is managed by ventilation, intubation and mechanical ventilation, the following adverse effects are possible:

1. CVS:
    - Bradycardia, can occur as a direct effect on myocardial cholinergic receptors.
        - ♥ This is more likely if a second dose is repeated within 15 minutes.
        - ♥ It is more commonly seen in children
2. Rhabdomyolytic like effects:
    - Hyperkalemia:
        - ♥ May be seen in association with crush injuries, or burns (deep enough to involve muscle), in delayed presentations.
        - ♥ May be seen from 20-120 days post a spinal cord transection.
        - ♥ May be seen in chronic denervation neurological disease.

        The hyperkalemic effect is transient, peaking at around 5 minutes and lasting up to 15 minutes, post suxamethonium administration.
    - Myoglobinemia
3. Prolonged paralysis:
    - Myasthenia gravis
    - **Pseudocholinesterase deficiency:**

        Inherited plasma cholinesterase deficiency:[1]

- ♥ Homozygotes (< 0.05% of the population) may remain apnoeic for 1-2 hours after receiving IV suxamethonium and develop a dual (phase II) block during this time

- ♥ Heterozygotes (3.8% of the population) have little or no disturbance and may remain apnoeic for approximately 10 minutes after IV administration.

4. Malignant hyperthermia.

5. Suxamethonium myalgias:

   - These are primarily felt around the **neck, chest** and **shoulders.**

   - They occur more commonly in patients who have been allowed to ambulate within 24 hours of their anaesthetic.

   - They are not related to the degree of observed fasciculations.

   - The incidence of this reaction can be reduced by the prior administration of a small dose of a non-depolarizing relaxant.

   - The incidence is more common in females and less common in children.

   - Severity of symptoms can range from mild to quite severe.

   - Symptoms generally only last **1 - 2 days.**

6. Raised compartmental pressure effects:

   These include:

   - Raised intracranial pressure:

     - ♥ This is **not** a contraindication however for use in head injured patients. The risk is more theoretical, and thus is outweighed by the far greater risk of hypoxia and secondary cerebral injury in a significantly head injured patient.

   - Raised intraocular pressure:

     - ♥ Rises of up to 8 mm Hg, probably caused by extra-ocular muscle fasciculation.

       This may result in vitreous loss if the anterior chamber is open.

   - Raised gastric pressure:

- ♥ Up to 85 mmHg, maximal during fasciculation

7. Phase II Blocks:

   - When suxamethonium is administered over a prolonged period or in repeated doses the characteristics of the neuromuscular block may change from the characteristic depolarising type to one *resembling a non-depolarising block*, (termed a "Phase II" block).

   - Neostigmine may partially reverse a phase II block, (but enhances Phase I or depolarizing blocks).

8. Allergic reactions - true anaphylaxis is rare.

Dosing

Adults:

- **1 - 1.5 mg /kg IV bolus.**

- IM, up to **2.5 mg/kg**, maximum dose 150 mg [1], (however **IV** is the preferred route of administration).

Child:

- IV bolus 1 mg/kg for intubation. [1]

Neonate and infant:

- IV bolus 2 mg/kg for intubation. [1]

Note: in children, there is a risk of bradycardia and asystole particularly if there is hypoxia. Suxamethonium should be given with atropine.

References

1. Suxamethonium in Australian Medicines Handbook, July 2013.

2. Suxamethonium in RCH Pharmacopeia, Accessed December 2013

3. Suxamethonium in MIMs October 2013.

4. Suxamethonium in Paul Young, Critical Care Drug Manual, Wellington Hospital Intensive Care Unit, 2010.

5. Developing Anesthesia; Dr David Pescod, V1.6, 2007

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Reviewed April 2017.