MUSCLE RELAXATION AND MUSCLE RELAXANTS

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Lecture Contents

- History of neuromuscular blockade
- Brief review of neuromuscular junction
- Types and structures of neuromuscular blocking drugs
- Monitoring of neuromuscular blockade
- Problems with neuromuscular blockade
- Suxamethonium apnoea
- Ways to avoid neuromuscular blockade

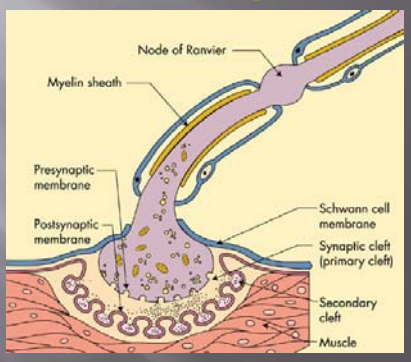
History - I

- Curare used for centuries by indigenous people of Amazon to hunt game
- Peter Martyr d'Anghera wrote of poisoned arrows in De Orbe Novo (1516)
- Sir Benjamin Brodie (1812) demonstrated that small animals could be kept alive after being injected with curare by inflating their lungs with bellows
- Claude Bernard (1846) proved that curare acted solely on the neuromuscular junction
- Harold King (1935) isolated d-tubocurarine from curare and established it was a rigid molecule with two quaternary ammonium groups at either end

History - II

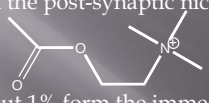
- Griffith & Johnson (1942) first used curare to paralyze a patient for appendicectomy:
  - "Every anaesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anaesthesia"
- Halton & Gray (1946) used Introcostrin on patients with good results. Gave rise to Liverpool technique – a triad of narcosis, analgesia and muscle relaxation

Neuromuscular Junction - I



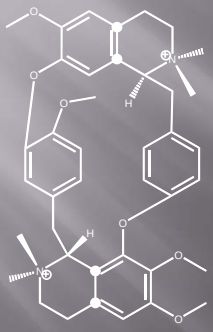
Neuromuscular Junction - II

- Acetylcholine (ACh) is the transmitter which interacts with the post-synaptic nicotinic receptors
- Structure is:

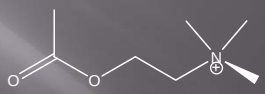


- Stored in the vesicles. About 1% form the immediately releasable store
- Each vesicle holds about 12,000 molecules of ACh
- ACh not binding to the receptors or released after binding are destroyed almost instantly by acetylcholinesterase (< 1 ms) in the secondary clefts, where it is attached to the basement membrane

Structure of d-Tubocurarine

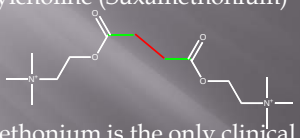


Compare with the structure of acetylcholine:



Other Muscle Relaxants – I

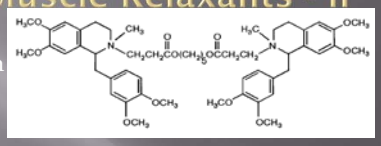
- Succinylcholine (Suxamethonium)



- Suxamethonium is the only clinical example of a DEPOLARIZING muscle relaxant. It has a rapid onset of action and, in most people, it wears off quickly (~ 5-10 min)
- Has many side-effects

Other Muscle Relaxants - II

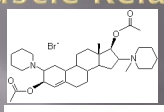
- Atracurium



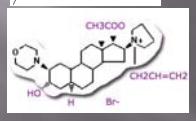
- It is a bisbenzyltetrahydroisoquinolinium salt
- Consists of 10 stereoisomers when synthesized
- Rationally designed in 1974
- Only common example of a non-steroidal NON-DEPOLARIZING muscle relaxant
- Breakdown not affected by hepatic or renal disease

Other Muscle Relaxants - III

- Vecuronium



- Rocuronium



- These are examples of steroidal-based muscle relaxants
- They act in a NON-DEPOLARIZING manner

Pharmacokinetics of Non-Depolarizing Agents - I

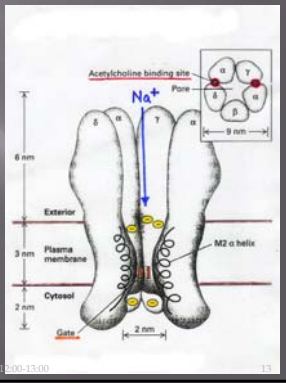
- Elimination half-life of atracurium is about 30 mins; elimination half-life of other agents is >60 mins
- Atracurium metabolised by Hofmann degradation and non-specific esterases, therefore not affected by hepatic or renal failure
- Vecuronium metabolised by deacetylation in the liver to 3-OH, 17-OH and 3,17-di-OH vecuronium; may be of clinical significance after prolonged dosing

Pharmacokinetics of Non-Depolarizing Agents - II

- Atracurium and vecuronium are largely (60-90%) protein bound to albumin so volume of distribution is small (~200 ml/kg)
- Both agents have charged nitrogen atoms so are not able to cross the blood-brain barrier
- Duration of action is prolonged by:
  - Hypokalaemia
  - Hypocalcaemia
  - Hypermagnesaemia
  - Hypoproteinaemia
  - Dehydration
  - Acidosis
  - Hypercapnia

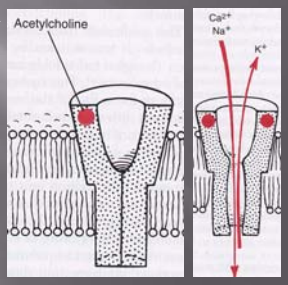
Action of Muscle Relaxants - I

- In previous slides, have had DEPOLARIZING and NON-DEPOLARIZING muscle relaxants
- To understand the difference, must recall the structure of the acetylcholine receptor:



Action of Muscle Relaxants - II

- Binding of one ACh molecule to one of two binding sites does not open the channel
- If ACh binds to both α-subunits simultaneously, the channel will open. Ions flow across the membrane



Action of NON-DEPOLARIZING Muscle Relaxants

- NON_DEPOLARIZING muscle relaxants bind to one of the α-subunits competitively.
- The receptor will not open, even if the other α-subunit is occupied by an acetylcholine molecule

Action of DEPOLARIZING Muscle Relaxants

- Suxamethonium binds simultaneously to *both* α-subunits, thereby activating the receptor
- Voltage-sensitive Na^+ channels open, then close and are inactivated
- Cannot open again until membrane potential is reset. No electrical impulses can be conducted
- Suxamethonium is *not* destroyed by acetylcholinesterase, but by pseudocholinesterase, in a relatively much slower reaction

Reversal of Blockade by Muscle Relaxants

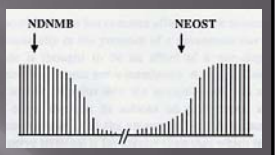
- NON-DEPOLARIZING muscle relaxants are competitive at the α-subunit
- Blocking the action of acetylcholinesterase (using an acetylcholinesterase inhibitor e.g. neostigmine) will extend the lifetime and concentration of ACh
- ACh will thus compete more effectively at the α-subunits and will reverse the block
- The DEPOLARIZING agent suxamethonium is very similar to ACh. It stays in the cleft and reacts repeatedly with the receptors. Extending the life of ACh will *not* reverse the block in this case

Clinical Monitoring of Neuromuscular Blockade

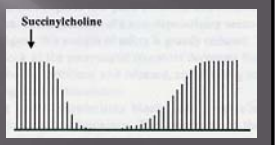
- If neuromuscular blockade is not reversed adequately in recovery, it may affect patient outcome
- Can use crude clinical assessment, such as sustaining head lift for > 5 sec
- Slightly more scientific way uses a nerve stimulator with a Train of Four (ToF) pattern of pulse stimulation. This is a more sensitive clinical test of reversal than just a set of pulses

NM Stimulation Patterns

- Pattern for a NDNMB with neostigmine reversal

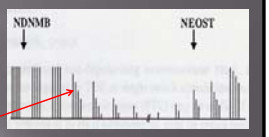


- Pattern for a DNMB:

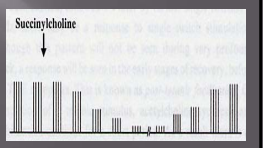


ToF Patterns

- NDNMB with neostigmine reversal:



- DNMB:

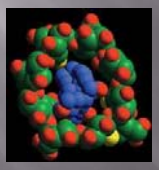


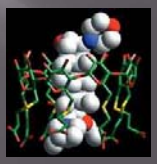
Fade

- Why is fade seen with NDNMBs but not with DNMBs?
- The NDNMBs bind to a pre-synaptic receptor which has a different combination of subunits to the post-synaptic receptor
- Causes less acetylcholine to be released each time the nerve is stimulated
- DNMBs do not bind to the pre-synaptic receptors

Reversal of Neuromuscular Blockade

- Common clinical method is to use a competitive inhibitor of acetylcholinesterase (usually neostigmine)
- Newer method uses a *cyclodextrin* (sugammadex) to effectively bind strongly to the NDNMB rocuronium:





Problems with Neuromuscular Blockade - I

- Problem of most concern to anaesthetists and surgeons is awareness
- Incidence is probably about 1:1000 anaesthetics if one looks hard enough but for certain procedures may be higher
- If patient has NMB on board, then cannot move to let anyone know

Problems with Neuromuscular Blockade - II

- Suxamethonium is commonly used to allow intubation
- Very "dirty" drug:
  - Hyperkalaemia
  - Increased intra-ocular and intra-cranial pressure
  - Muscle pains
  - Masseter spasm
  - Malignant hyperthermia
  - "Sux apnoea"

Suxamethonium Apnoea

- Causes prolonged neuromuscular blockade – from 30 mins to 6 hours!
- Results from different forms of pseudocholinesterase, which breaks down suxamethonium
- Rarely, patients may have no pseudocholinesterase; these patients have very prolonged apnoea
- Autosomal recessive for the silent pseudocholinesterase gene

Ways to Avoid Problems with NMB

- Use rocuronium with sugammadex – expensive
- Avoid using NMBs altogether; some opioids are powerful enough to allow intubation without NMB
- However, there can be problems with such opioids; may give rise to difficulties ventilating patients
- If it is just required that the patient has regular breathing, then may be able to hyperventilate the patient, thus rendering them hypocarbic

SUMMARY

- Looked at difference between DEPOLARIZING and NON-DEPOLARIZING neuromuscular blockers
- Whilst structures are similar, mechanisms of action are quite different
- Reversal of the action of NON-DEPOLARIZING neuromuscular blockers can be performed with neostigmine
- Can often undertake surgery without the use of such agents

QUESTIONS?