

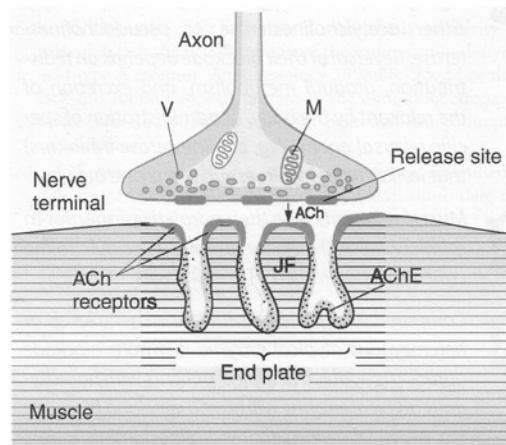
NEUROMUSCULAR BLOCKING AGENTS:

(a) *To explain the physiology of neuromuscular transmission and how this may be interfered with to produce muscle relaxation.*

(c) *To describe the post-junctional and pre-junctional receptors.*

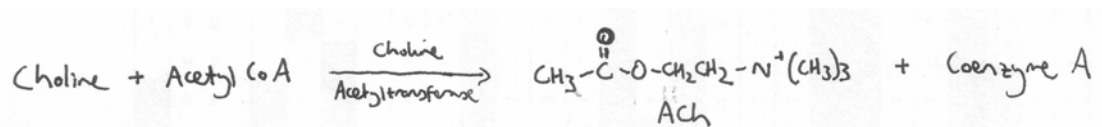
Neuromuscular Junction (NMJ):

- Neurochemical bridge between motor neuron and skeletal muscle fibre that consists of:
 - o (1) Unmyelinated prejunctional nerve terminal ending of an α -motor neuron
 - Contains apparatus vital to the synthesis, storage and release of ACh – Includes several ACh-containing vesicles, mitochondria, ER
 - Also possess presynaptic nAChRs that help regulate ACh release
 - o (2) Post-junctional motor-end plate of the skeletal muscle fibre
 - Highly folded and specialised postjunctional membrane of skeletal muscle fibre that contains – (a) Post-synaptic junctional nAChR at the crests of the folds (at a very high density of ~ 5 million), and (b) AChE at the troughs of the folds
 - o (3) Synaptic cleft
 - 20 nm wide space containing ECF that separates (1) and (2)



Nicotinic Cholinergic Transmission at the NMJ:

- ACh is a quaternary ammonium ester neurotransmitter that is synthesised in the axoplasm of the motor nerve terminal – It is formed by the acetylation of Choline (derived from diet or recycled from ACh metabolism) with Acetyl-CoA using the enzyme Choline acetyltransferase



- ACh is then stored in several synaptic vesicles in the motor nerve terminal, which are then ready for release into the synaptic cleft via two means:
 - o (i) In absence of a motor nerve impulse – Random release of a single “quanta” of ACh into the synapse independent of nerve terminal depolarisation
 - o (ii) In response to a motor nerve impulse – A single nerve AP increases the nerve terminal MP from -90 mV at rest to $V_{\text{THRESHOLD}}$ of -45 mV causing it to depolarise. This activates nerve terminal Adenylyl cyclase to produce cAMP, which triggers opening of Ca^{2+} channels and an influx of Ca^{2+} . The rise in IC $[\text{Ca}^{2+}]$ causes vesicles to fuse with the membrane and exocytose ACh into the synaptic cleft. Note that a single nerve impulse will release > 200 quanta of ACh

Nb. 1 quanta of ACh = 100-200 synaptic vesicles = 5000-10,000 ACh molecules

- ACh diffuses across the synaptic cleft and binds to postjunctional nAChR on the motor-end plate:
 - o nAChR is a pentameric ligand-gated ion channel that is activated when ACh binds to both of its α -subunits – This results in Na^+ and Ca^{2+} influx, and K^+ efflux
 - o A random single quantal release of ACh (i.e. released in the absence of a motor nerve impulse) only produces a “Miniature EPP” (MEPP) of < 1 mV only, which is insufficient to activate perijunctional VG- Na^+ channels and trigger a muscle AP
 - o However, ACh released from a single motor nerve impulse is sufficient to stimulate enough nAChR to produce a summated motor EPP that can raise the MP of perijunctional sarcolemma from -90 mV at rest to $V_{\text{THRESHOLD}}$ of -45 mV. This triggers opening of perijunctional VG- Na^+ channels, rapid depolarisation of perijunctional sarcolemma, and generation of a skeletal muscle AP

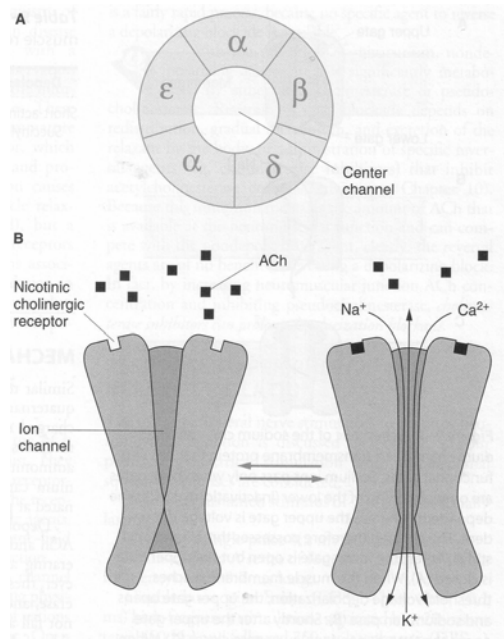
Nb. Only 10% of nAChR are needed to be activated ($> 500\text{k}$ nAChR) to produce an motor end-plate potential sufficient enough to depolarise the perijunctional membrane and cause a skeletal muscle AP

- The AP is propagated over the skeletal muscle fibre to the T-tubular system, which causes Ca^{2+} to be released from sarcoplasmic reticulum stores, which then induce excitation-contraction coupling and skeletal muscle contraction
- Relaxation of skeletal muscle fibre occurs relies on:
 - o (a) Acetylcholinesterase (aka. True cholinesterase)
 - Found in troughs of postjunctional folds
 - Main role is to limit effect of ACh on nAChR – Rapidly and efficiently hydrolyses ACh (4000 ACh/sec such that only 50% of released ACh binds nAChR), thus preventing sustained MEP depolarisation
 - Contains (i) anionic binding site – Binds +vely charged quaternary ammonium on ACh, and (ii) esteratic binding site – Hydrolyses ester link in ACh to release choline (which is taken up into nerve terminal) and causes AChE to be acetylated. Acetylated AChE is rapidly hydrolysed to release acetic acid and regenerate the enzyme
 - o (b) Closure of postjunctional nAChR ion channel and repolarisation of the MEP
 - o (c) Resetting of VG- Na^+ channels in the perijunctional membrane reset
 - o (d) Sequestration of Ca^{2+} in the SR

Nicotinic ACh Receptors (nAChR):

- Structure and function of nAChR:
 - o Transmembrane ligand-gated ion channel – Pentameric structure ($2\times \alpha, \beta, \delta, \gamma$ or ϵ subunits – depending on adult/foetal subtype) with a central ion channel pore (that permits transmembrane flow of $\text{Na}^+, \text{Ca}^{2+}, \text{K}^+$) and an extracellular receptor (that binds ACh)
 - o Simultaneous binding of the two α subunits by an ACh each causes a brief conformational change in the receptor. This opens the central ion channel and permits Na^+ and Ca^{2+} influx and K^+ efflux along their electrochemical gradients – In skeletal muscle, this ion flux produces a localised membrane depolarisation (or end-plate potential), which can summate and trigger a skeletal muscle AP (via activation of perijunctional VG Na^+ channels) if $V_{\text{THRESHOLD}}$ of -45 mV is reached
 - o When there is absence of ACh binding to the receptor, the central ion channel remains in a closed state (stabilised by $\delta\epsilon$ subunits in adult subtype) and there is a lack of ion flux across the membrane

Note: This describes post-synaptic nAChR (junctional and extrajunctional). Pre-synaptic nAChR are structurally and functionally different (See below)



- There are two subtypes of nAChR – (i) Foetal nAChR and (ii) Adult nAChR
 - Structurally, foetal and adult nAChR are both pentameric and very similar except for a difference in a single subunit (ϵ vs γ) – Foetal nAChR contains 2x α , β , δ and a γ ; Adult nAChR contains 2x α , β , δ and a ϵ
 - Functionally, foetal nAChR differs from adult nAChR in that when activated by ACh, it is associated with a more prolonged opened ion channel state (allowing Na^+ , Ca^{2+} , K^+ flow across their electrochemical gradients), which has two implications – (i) A single quanta of ACh can elicit a muscle AP, and (ii) Greater release of K^+ from muscle (contributes to hyperkalaemic response to denervation)
 - Foetal nAChR usually disappears and adult nAChR is expressed during synaptic maturation, HOWEVER with denervating conditions, foetal nAChR can be upregulated in extrajunctional areas of the skeletal muscle membrane
- NMJ contains 3 types of nAChR:
 - Two postsynaptic on skeletal muscle surface:
 - (i) Junctional nAChR
 - Located on the crest of the specialised post-junctional folds (directly opposite sites on nerve ending where ACh is released) and implicated in normal NMJ transmission
 - ~ 5 million receptors in the adult form (of which only 10% are needed to be stimulated to cause a muscle AP) – They can be upregulated (in response to SC injury, CVA, burns, prolonged immobility, MS, GBS, prolonged NMBD exposure) or downregulated (in response to myasthenia gravis, AChE overdose, OP poisoning)
 - (ii) Extrajunctional nAChR
 - Appear over entire post-junctional membrane (rather than confined to specialised motor end plate)
 - Present in small numbers as synthesis is suppressed by neural activity – They proliferate when loss of motor nerve activity due to a denervating event, but degenerate when neural activity returns
 - Mainly in foetal form (and highly responsive to activation by ACh (or SCh))
 - Presynaptic on nerve ending:
 - Prejunctional nAChR
 - Differs from postsynaptic nAChR structurally (has a different pentameric structure) and functionally (altered chemical binding

characteristics, ion channel selectively (I.e. Na^+ but not Ca^{2+}), and preferential blockade during high-frequency stimulation)

- Main role is to influence presynaptic vesicular release of ACh – Stimulation of nAChR helps mobilise further ACh vesicles for release as part of a +ve feedback loop

- (b) *To describe depolarising and non-depolarising block.*
- (d) *To outline the properties of an ideal neuromuscular blocking agent.*
- (f) *To give a detailed account of the pharmacology of suxamethonium including its undesirable properties.*
- (g) *To describe the pharmacokinetics of the neuromuscular blocking agents. To describe the clinical implications of the pharmacokinetic differences.*
- (h) *To describe the pharmacodynamics of the non-depolarising muscle relaxants with particular reference to cisatracurium, atracurium, rocuronium, vecuronium, mivacurium and pancuronium.*
- (i) *To describe the physiological and pathological factors that may modify responses to muscle relaxants.*
- (j) *To describe the adverse effects of muscle relaxants.*
- (k) *To describe the physiological and pathological factors which may affect recovery from neuromuscular blockade.*

(A) Introduction of Neuromuscular Blocking Drugs

Overview of Neuromuscular Blocking Drugs (NMBD):

- NMBD interrupt transmission of nerve impulses at the NMJ to produce skeletal muscle relaxation
- They are categorised as follows:
 - (1) Depolarising NMBD – Mimic the actions of ACh to produce phase 1 or phase 2 depolarising neuromuscular blockade. Succinylcholine (SCh) is the only depolarising NMBD used clinically
 - (2) Nondepolarising NMBD – Interfere with the actions of ACh to produce nondepolarising neuromuscular blockade. There are several types:
 - (a) Long-acting – Pancuronium, Doxacurium, Pipercuronium (all aminosteroids)
 - (b) Intermediate-acting – Atracurium and Cisatracurium (as benzyloisoquinolines); Vecuronium and Rocuronium (as aminosteroids)
 - (c) Short-acting – Mivacurium (as a benzyloisoquinoline)
- NMBD have several clinical uses:
 - (i) Facilitate tracheal intubation – This requires administration of 2x ED₉₅
 - (ii) Facilitate surgical working conditions during GA – This requires 90% suppression of single-twitch response
 - (iii) SCh (at 0.1 mg/kg IV) is used to treat laryngospasm
 - (iv) Facilitate mechanical ventilation in ICU (I.e. ARDS, suppression of spontaneous ventilation, tetanus, Etc.)
- Selection of a NMBD depends on the following factors:
 - (i) Required speed of onset – If rapid and brief onset of muscle relaxation for tracheal intubation, SCh is used (or alternatively, rocuronium with similar brief onset BUT prolonged duration of action); otherwise any nondepolarising NMBD can be used
 - (ii) Required duration of action – If sustained muscular relaxation is needed, intermittent doses or continuous infusions of an intermediate-acting nondepolarising NMBD can be used; brief periods of relaxation can be achieved with SCh or short-acting ND NMBDs

- (iii) Balance of beneficial and side-effects – Histamine release (esp benzylisoquinolines), increased HR (pancuronium), safe in renal/liver failure (Eg. atracurium, cisatracurium), anaphylaxis (Eg. SCh, rocuronium), lack of circulatory effects (Eg. vecuronium, rocuronium, cisatracurium), Etc.

Properties of an Ideal NMBD:

- Physico-chemical properties:
 - Cheap to produce
 - Simple preparation with a water-soluble formulation
 - Stable in solution
 - Has a long shelf-life at room temperature and no special storage requirements
 - Compatible with other drugs and fluids
- Pharmacokinetic properties:
 - Short duration of action, non-cumulative and is suitable for infusion
 - Complete and rapid clearance (excretion and metabolism) from body – Metabolism to inactive and non-toxic products; organ-independent clearance such that it can be used in renal/hepatic failure
 - Unable to cross BBB or placenta
- Pharmacodynamic properties:
 - Rapid and predictable onset (within one circulation time)
 - Predictable offset that can be easily antagonised by a conventional reversal agent (AChEi or sugammadex)
 - High potency and efficacy at causing NMB with a predictable dose-effect response
 - Non-depolarising mechanism of action
 - Actions confined to NMJ, thereby minimising unwanted systemic effects (esp CVS effects such as haemodynamic changes and arrhythmias, respiratory effects (such as bronchospasms), histamine release, altered electrolyte balance, and raised IAP, ICP or IOP)
 - Safe to use in children and in pregnant women
 - Nil anaphylaxis or anaphylactoid reactions
 - Not a MH trigger
 - Nil critical illness myopathy with prolonged infusions

Structure-Function Activity of NMBD:

- ACh is a quaternary ammonium ester whereby the +vely charged quaternary ammonium group is responsible for binding to the –vely charged α -subunits on nAChR
- All NMBDs have at least 1 quaternary ammonium group that becomes protonated (or +vely charged) at physiological pH (I.e. resembling that of ACh) – This permits its binding to the –vely charged α -subunits on nAChR:
 - Monoquaternary ammonium agents – Vecuronium and Rocuronium
 - Bisquaternary ammonium agents – SCh, Pancuronium, Mivacurium, Atracurium, Cisatracurium

Note: The highly ionised state of NMBDs at physiological pH (due to the +vely charged ammonium groups) means that they have:

- (i) High water solubility
- (ii) V_D limited to $\sim$ ECFV (0.2 L/kg)
- (iii) Little plasma protein binding (up to 50%)
- (iv) High plasma concentration in ionised form
- (v) Inability to cross lipid membrane barriers (BBB, GIT, placenta, renal tubules)

- The binding of NMBD to nAChR causes either:
 - (i) Competitive inhibition of nAChR (non-depolarising NMBDs) – Bulky and rigid molecules cannot activate nAChR and also prevent ACh from binding to and activating nAChR

- (ii) Partial agonist effect on nAChR (depolarising NMBDs) – Binding to nAChR causes receptor activation
- Note – This binding also occurs at other cholinergic sites (Eg. nAChR at ANS ganglia and mAChR at PNS effector cells), which leads to side-effects (esp CVS effects)

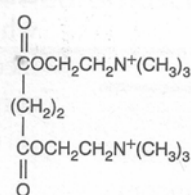
Note: Allergic reactions (anaphylactic and anaphylactoid) 2° to NMBDs are due to the presence of the quaternary ammonium group:

- Sch is the most likely agent to cause an allergic reaction, followed by rocuronium, vecuronium and other agents
- Reactions after first exposure can be due to cross-sensitisation with cosmetics/soaps that possess an antigenic quaternary ammonium group

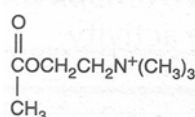
- Structures of NMBDs:

○ Sch

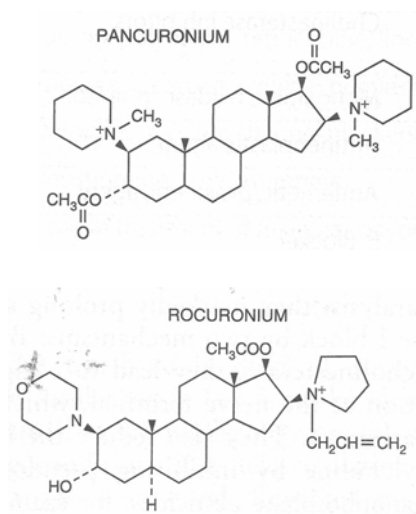
SUCCINYLCHOLINE



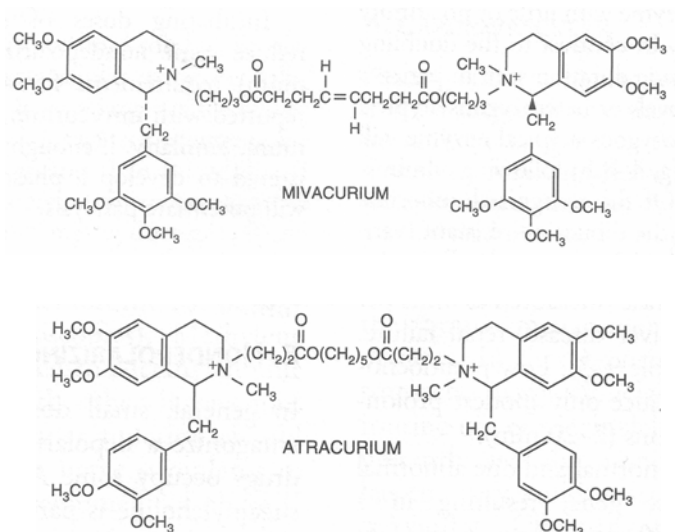
ACETYLCHOLINE



○ Aminosteroids



○ Benzyloquinolines



Nb. Cisatracurium is one of ten isomers of atracurium

Descriptors of NMBD Clinical Effects:

- ED₉₅
 - o Median dose needed to produce 95% depression in height of a single twitch response in subjects (I.e. in 50% of subjects). Of note, this is measured in the presence of a N₂O-barbiturate-opioid anaesthesia
 - o Used to assess potency of NMBD, such that equipotent NMBD will have equivalent ED₉₅'s
- Onset of action – Time from injection to onset of maximal single-twitch depression
- Duration of action – Time from injection to return of single twitch height to either 25% or 95%
- Recovery index – Time from 25% to 75% return of a single-twitch height
- Clinical duration – Time from injection to recovery of TOF to either ≥ 0.7 or ≥ 0.9

Muscle Relaxation at Different Muscle Groups:

- Muscle relaxation will vary at different muscles groups such that when a NMBD is administered, a “Paralytic march” is described in textbooks in the following order with onset, and in the reverse order with recovery:

Extrinsic eye muscles → Small facial muscles → Limbs → UAW and Larynx → Respiratory muscles

- However, clinically when a NMBD is given the onset/offset of muscle groups follow a different pattern:
 - o (i) Central muscles (diaphragm, intercostal, larynx, facial/eye muscles) have the fastest onset and offset (mainly due to good regional blood flow)
 - o (ii) Peripheral muscle (adductor pollicis) have the slowest onset and offset (mainly due to poor regional blood flow)
 - o (iii) UAW muscles (Eg. pharynx) have fast onset similar to central muscles BUT slower offset similar to peripheral muscles (mainly due to sensitivity to NMBD)

In summary:

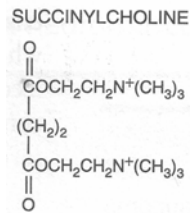
- Onset: Larynx, Facial/Eye, UAW muscles → Respiratory muscles → Adductor pollicis
- Offset: Respiratory muscles → Larynx, Facial/Eye, UAW muscles → Adductor pollicis

- The reasons for the varying onset/offset in different muscle groups are due to:
 - o (i) Differences in regional blood flow (I.e. more to central muscles)
 - o (ii) Muscle size, fibre/twitch type, and innervation
 - o (iii) Muscle temperature (I.e. cooler in peripheries)
 - o (iv) Differences in dose requirements (facial muscle, diaphragm, jaw and larynx/glottic muscles have a higher ED₉₅ for relaxation than the adductor pollicis, such that the dose of NMBD to block the diaphragm is twice that to produce similar effect at adductor pollicis)

(B) Depolarising Neuromuscular Blocking Drugs: Succinylcholine

Structure and Preparation of Succinylcholine (SCh):

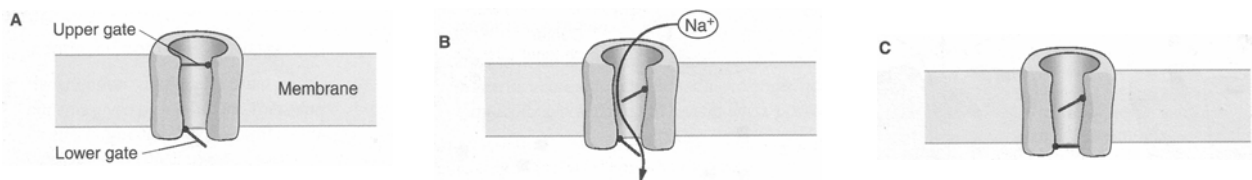
- Structure – Diacetylcholine (two molecules of ACh bound together via an acetate methyl group). Also a dicholine ester of succinic acid



- Preparation – Clear and colourless solution of succinylcholine chloride (50 mg/mL). Needs to be stored at 4°C

Mechanism of Action of SCh:

- Mechanism of phase 1 depolarising NM blockade:
 - SCh acts as a partial agonist at postjunctional nAChR – At least 1 SCh bind to an α subunit of nAChR (other α subunit can be occupied with SCh or ACh) and activates it → Produces a conformational change in the receptor-channel complex that results in ion flux across the membrane (Na^+ , Ca^{2+} influx; K^+ efflux) → Depolarises MEP → Triggers activation of perijunctional membrane VG- Na^+ channels (open channel's upper gate) and causes Na^+ influx → Produces a muscle AP → VG- Na^+ channel's lower gate closes after a limited period of time and Na^+ influx halts, thus terminating muscle AP (Note: VG Na^+ channel remains in this inactivated state (upper and lower gates closed) until the MEP repolarises)



- Since SCh is not hydrolysed by AChE, it has a prolonged presence in the NMJ → Continues to activate several other nAChR via above process and produce ongoing muscle AP → Cause sustained muscle contractions (or fasciculations)
 - Muscle relaxation is caused by persistent activation of nAChR and sustained MEP depolarisation → Prevents resetting of the perijunctional VG- Na^+ channels (I.e. reclosure of upper gate and reopening of lower gate) → Thus, subsequent release of ACh from the motor nerve ending is unable to trigger produce a muscle AP, thus resulting in muscle relaxation
 - Note that SCh also has an effect on prejunctional nAChR but its role is minor
- Mechanism of phase 2 depolarising NM blockade:
 - SCh acts similar to a non-depolarising NMBD – Prevents postjunctional nAChR response to ACh, even when the MEP has repolarised
 - Mechanism is unknown – Possible nAChR desensitisation, ion channel blockade, intracellular effects of SCh in skeletal muscle

For both phase 1 and 2 depolarising NMB, ONLY 10-20% receptor occupancy is required by SCh for a decrease in twitch height!

- Return of NMJ function occurs due to clearance of SCh from synaptic cleft through diffusion into ECF, and not via rapid hydrolysis by plasma cholinesterase per se (Note – Metabolism by plasma cholinesterase influences the duration of action of SCh by influencing the amount of drug hydrolysed prior to reaching the NMJ)

Clinical Uses and Effects of SCh:

- Clinical uses of SCh – It is used when intense paralysis is needed to be produced rapidly and only for a brief period of time:

- (1) Rapid tracheal intubation (within 30-60 sec) as part of RSI – Nb. Its short duration of action (3-5 mins) also prevents arterial hypoxia prior to return of spontaneous ventilation in a well pre-oxygenated patient in a CVCI situation
- (2) Used as an infusion to facilitate short surgical procedures
- (3) Modify fits for ECT
- Dose, onset and duration of action of SCh:

ED₉₅ of SCh: 0.27 mg/kg IV

 - Traditional dose of 1 mg/kg IV (2 mg/kg IV in children) or 3-3.5x ED₉₅
 - Rapid onset within 30-60 secs – Due to its low lipid solubility and low potency, meaning that large doses are given
 - Short duration of action of 3-5 minutes – Due to rapid hydrolysis of SCh by plasma cholinesterase, such that 80-90% of IV dose metabolised prior to reaching NMJ
 - Lower dose of 0.6 mg/kg IV (or 2x ED₉₅) – Still produces suitable intubating conditions, BUT reduces duration of action by > 1.5 minutes (I.e. more safety margin against hypoxaemia)
 - Larger dose of 1-1.5 mg/kg IV (or 3.5-4x ED₉₅) – Indicated when complete NMB is critical (I.e. as part of RSI)
 - IM dose is 2 mg/kg (or 4 mg/kg in children)
 - SCh infusion (1 g in 500 mL) or repeated small boluses can be used for procedures requiring brief but intense paralysis – Requires nerve stimulator monitoring to prevent overdose and phase II block
- Characteristics of phase 1 and phase 2 depolarising NMB:
 - Phase 1 depolarising block – Occurs with a single dose of SCh (< 2 mg/kg IV)
 - Clinical – Skeletal muscle fasciculation
 - Peripheral nerve stimulation
 - (i) Decreased contraction in response to single twitch stimulation
 - (ii) No tetanic fade – Decreased amplitude but sustained response to continuous stimulation (or tetany)
 - (iii) No fade with TOF (TOFR > 0.7) or DBS, but amplitude is decreased
 - (iv) Absence of posttetanic facilitation
 - (v) Augmentation of NMB after administration of AChEi
 - Phase 2 depolarising block – Occurs with a large single dose (> 2 mg/kg IV), repeated doses or continuous infusions of SCh. Its features clinically and on peripheral nerve stimulation resemble that of non-depolarising NM blockade
- Reversal of a depolarising block by SCh:
 - No suitable reversal agents exist, thus they require spontaneous reversal via clearance of SCh away from the NMJ via gradual diffusion into plasma (and then metabolised by plasma cholinesterase)
 - If a reversal agent (AChEi) is given, the depolarising block can be prolonged in a phase 1 block (since AChEi inhibits plasma cholinesterase and prevents SCh metabolism); however, it can reverse a phase 2 block

Metabolism and Clearance of SCh:

- (1) SCh is cleared from the body mainly via hydrolysis by plasma cholinesterase:
 - SCh is hydrolysed into Succinylmonocholine (weak active metabolite with < 1/20th as SCh), which is then further hydrolysed to succinic acid and choline
 - Rate of hydrolysis is so rapid and efficient such that only 10-20% of IV SCh reaches the NMJ – This causes SCh to have a brief duration of action (3-5 mins)

Note: "Plasma (or pseudo or butyryl) cholinesterase":

- Encoded by a single gene on chromosome 3
- Tetrameric glycoprotein enzyme (4x identical subunits, each with an active catalytic site) that is synthesised in the liver and found in plasma
- Metabolises several drugs – SCh, Mivacurium, Ester LA and Aspirin

Note – Duration of action of SCh is principally influenced by the rate at which plasma cholinesterase hydrolyses SCh, which then determines the amount of SCh that reaches the NMJ. The offset or recovery from SCh is then determined by its diffusion away from NMJ into ECF

- (2) A small amount of SCh (< 10%) is excreted unchanged in the urine

Adverse Effects of SCh:

- (1) Cardiac dysrhythmias
 - o Sinus bradycardia, junctional rhythm, and sinus arrest – Due to partly active succinylmonocholine metabolite sensitising the mAChR in SA node to succinylcholine (occurs in children on the first dose of SCh; occurs in adults when second dose given within 10 mins of the first). May be prevented by pretreating with atropine
 - o Increased HR and hypertension – Due to ganglionic nAChR stimulation
- (2) Hyperkalaemia
 - o A transient (< 15 mins) and small rise in serum K^+ (0.5 mmol/L) occurs due to K^+ efflux into ECF from muscle cells during muscle depolarisation
 - o However, an excessive rise in serum K^+ leading to severe hyperkalaemia and precipitating cardiac arrest is known to occur in certain groups of patients after being given SCh:
 - (i) Clinically unrecognised muscular dystrophy in male paediatric patients (esp Duchenne or Becker muscular dystrophy)
 - (ii) Unhealed 3rd degree burn – Due to upregulation of extrajunctional foetal nAChR
 - (iii) Denervation conditions (CVA, spinal cord injuries, para- and hemiplegia, GBS, MS, polyneuropathy, tetanus, severe Parkinson's disease) – Due to upregulation of extrajunctional foetal nAChR
 - (iv) Severe skeletal muscle trauma
 - (v) Severe abdominal infections
 - (vi) Metabolic acidosis and hypovolaemia

Pre-existing hyperkalaemia and renal failure per se are not contraindications to SCh use, BUT there is risk of producing rises in serum K^+ to levels where there is a high risk of cardiac arrhythmias!

- (3) Post-operative myalgia (neck, back and abdomen) – Esp in young adults and females
- (4) Myoglobinuria – Due to damage of skeletal muscle from fasciculations (mainly in paediatric patients)
- (5) Increased intraabdominal and intragastric pressures
 - o Related to intensity of fasciculations
 - o Although IGP is raised by 10 cmH₂O, the LOS sphincter tone is increased as well such that the risk of reflux (and aspiration) is negated – HOWEVER, if a pre-treatment with a non-paralysing dose of ND NMBD is given, the aspiration risk increases as LOS sphincter tone decreases!
- (6) Increased intraocular pressure
 - o Raised IOP (by 10 mmHg) is transient (only minutes) but carries risk of extrusion of global contents in the setting of an open eye injury

- Due to contraction of extraocular muscles causing globe compression, and transient dilation of choroidal blood vessels
- (7) Increased intracranial pressure
 - Due to increased cerebral activity and CBF 2° stimulation of muscle stretch receptors from fasciculations
- (8) Masseter jaw rigidity
 - Transiently sustained skeletal muscle contraction of the jaw/masseter usually occurs in children – It can interfere with DL and mask ventilation, and can be associated with MH
- (9) Malignant hyperthermia – SCh is a potent trigger (See topic on MH for more details)
- (10) Fatal anapylactoid and anaphylaxis reactions due to the quaternary ammonium group – SCh is the most likely muscle relaxant to cause these. Reactions upon first exposure can be due to cross-sensitisation with cosmetic/soaps with quaternary ammonium groups
- (11) Histamine release
- (12) Prolonged paralysis or “Sux Apnoea” (See below)

A number of adverse effects of SCh can be attenuated or prevented by pre-treatment of a non-paralysing dose of non-depolarising NMBD. They include – (i) Cardiac dysrhythmias, (ii) Post-op myalgias, (iii) Raised IAP/IGP, (iv) Raised IOP, and (v) Raised ICP

Prolonged Paralysis due to SCh (Sux Apnoea):

- Prolonged NMB 2° to SCh is due to slowed or absent metabolism of SCh caused by:
 - (1) Quantitative deficiency in plasma cholinesterase (PC)
 - Reduced hepatic synthesis of PC due to severe liver disease or malnutrition
 - (2) Qualitative deficiency in PC (Ie. normal quantities but reduced PC activity)
 - (a) Drug-induced – All AChEi (EXCEPT edrophonium), Chemotherapy agents (esp cyclophosphamide), Metoclopramide, Ester LA (compete with other drugs for PC), OCP, Ketamine, Lithium, Pancuronium, Esmolol, and Tacrine
 - (b) Disease states – Renal failure (esp on dialysis), cardiac failure, TTX, cancer states, burns
 - (c) Hypothermia
 - (d) Pregnancy (oestrogen depresses PC activity from 1st TM until 6 weeks post-partum)
 - (e) Genetically-aberrant atypical PC
- Overview of “genetically-aberrant atypical PC”:
 - Often recognised when conventional SCh doses (IV 1 mg/kg) cause prolonged NM blockade (1-3 hrs)
 - Single gene locus on chromosome 3 encodes PC – A nucleotide alteration in this gene leads to a single amino acid substitution that can produce several variants in enzyme activity
 - There are four alleles involved:
 - (i) Usual (normal) allele (Eu)
 - Eu/Eu (DN80/FN60) – Normal SCh response (3-5 mins) – 96% prevalence
 - (ii) Atypical (dibucaine-resistant) allele (Ea)
 - Ea/Ea (DN20) – Greatly prolonged block (> 3 hrs) – 1:3200
 - Eu/Ea (DN40-60) – Slightly prolonged block (30 mins) – 1:480

“Dibucaine number” (DN):

- DN is the % inhibition of normal PC activity in metabolising benzylcholine substrate in the presence of 10^{-5} mol/L dibucaine (an amide LA)
- DN is proportional to the level of PC function in hydrolysing SCh – DN80 means normal PC, while DN20 means homozygous atypical PC variant, and DN40-60 means heterozygous atypical PC variant
- Note – DN does NOT reflect the quantity of enzyme in plasma (only its quality), thus reduced PC levels (i.e. liver disease) will have a DN80 but prolonged SCh duration of action

▪ (iii) Fluoride-resistant gene

- Ef/Ef (DN70/FN35; 1:150,000) and Ef/Ea (DN45/FN35; 1:20,000) – Greatly prolonged blocks (2-3 hrs)
- Ef/Eu (DN75/FN50) – Slightly prolonged block – 1:200

“Fluoride number” (FN) is the % inhibition of normal PC in metabolising benzylcholine when 50 mM Na fluoride is added. FN60 means normal PC, while FN35 means homozygous fluoride-resistant enzyme

▪ (iv) Silent (absent) type

- Es/Es (1:100,000) is the most severe form of mutation as the enzyme lacks activity (and reversal of SCh depends on its renal excretion!) – Causes up to 8 hours of paralysis after single dose!
- Es/Ea (1:30,000) and Es/Ef (1:150,000) also produce greatly prolonged paralysis
- Eu/Es (1:90) produces a slightly prolonged block

- Management – Patients should remain anaesthetised and mechanically ventilated while the NMB naturally wears off and muscle function returns. Administration of FFP (containing source of PC) can reverse the block BUT carries risks associated with a transfusion!

Aside: Enhanced PC activity leading to decreased NM blockade

- (1) Genetic – Inherited C5 isoenzyme
- (2) Obesity – More PC activity
- (3) Myasthenia gravis – Less functional nAChR that are less responsive to ACh

Interaction of ND NMBDs and AChEi with SCh:

- AChEi given during a phase I block prolongs paralysis due to SCh because of – (i) Inhibition of PC metabolism of SCh, and (ii) Increased synaptic ACh that further depolarises the MEP
- ND NMBD given during (i) Phase 1 block causes antagonism of the block (due to competition with SCh for nAChR), (ii) Phase 2 block causes potentiation of the block (due to unknown mechanism)
- Pancuronium is the only ND NMBD can prolongs paralysis due to SCh 2° to inhibition of PC activity

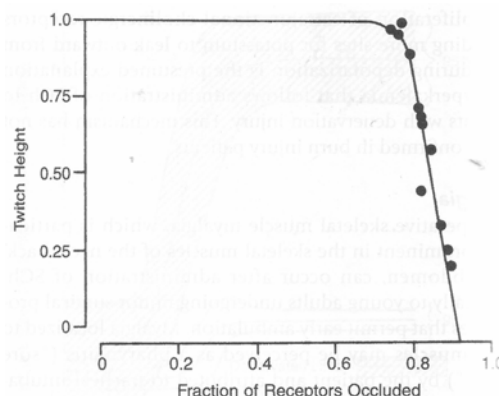
(C) **Non-Depolarising Neuromuscular Blocking Drugs (ND NMBD):**

Types of ND NMBD:

- (1) Benzylisoquinolines (atracurium, cisatracurium, mivacurium) – These are generally associated with more histamine release (I.e. bronchospasm, skin flushing, hypotension due to peripheral vasodilation)
- (2) Aminosteroids (rocuronium, vecuronium, pancuronium) – These are generally associated with more vagolytic responses

Mechanism of Non-Depolarising NMBD:

- ND NMBD mainly act as competitive inhibitors of postjunctional nAChR:
 - o They bind to at least a single α -subunit of nAChR (other α -subunit can be bound by ND NMBD or ACh) $\rightarrow$ ND NMBD lack agonist activity at nAChR $\rightarrow$ Receptor-channel complex does not undergo a conformational change and channel remains closed $\rightarrow$ No ion flow across membrane, thus preventing production of EPP and muscle AP
 - o They directly compete against ACh binding to nAChR such that if enough nAChR are bound by ND NMBD, there is lack of EPP and muscle AP production, and muscle relaxation occurs
- Alternate mechanisms include:
 - o (i) At large doses, they can enter nAChR-associated ion channel and block them $\rightarrow$ Directly inhibit ion flow across membrane
 - o (ii) Competitive inhibition of prejunctional nAChR
- NMJ transmission is inhibited ONLY when $>75\%$ of receptors are blocked by ND NMBD – This offers a wide safety margin as only a small number of nAChR at the NMJ are needed to summate a MEPP required to trigger a muscle AP and cause muscle contraction!



- Return of NMJ function is dependent on probability of ACh binding nAChR:
 - o This is influenced by the (i) Relative ratio of [ACh]:[ND NMBD] in the synaptic cleft, and (ii) Relative affinity of ACh to nAChR (relative to ND NMBD)
 - o Thus, if there are more ACh than ND NMBD (such as when ND NMBD diffuses away into ECF from NMJ and/or AChEi agent is given), then competitive inhibition of nAChR by the ND NMBD can be overcome

Clinical Uses and Effects of ND NMBD:

- Use of ND NMBD for intubation – They are generally not as rapidly and short acting as Sch. However, their onset can be accelerated by either:
 - o (i) Using a larger single dose ($> 2X ED_{95}$) – Rocuronium at $3-4x ED_{95}$ has similar onset as Sch, BUT this prolongs the duration of block, makes reversal more difficult, and is associated with more side-effects of the agent
 - o (ii) Using a priming dose (esp for ND NMBD other than rocuronium) – Subparalytic dose (10% of ED_{95}) given, then a larger dose ($2-3x ED_{95}$) given 4 minutes later. The priming dose acts by binding to spare receptors, thus allowing the 2nd larger dose to have more effect. Although the priming dose does not cause clinically significant paralysis, it has issues – (a) Desaturation in patients with respiratory compromise, (b) Patient distress (dyspnoea, diplopia and dysphagia)

As a general rule – More potent the agent, the slower the speed of onset. This is because lower doses of potent drugs are needed, and hence less drug is available at the NMJ

- Use of ND NMBD for maintaining relaxation during surgery – NMJ function should be monitored to prevent inappropriate maintenance dosing by using:
 - (i) Clinical judgment (Eg. spontaneous movement or respiratory efforts)
 - (ii) Peripheral nerve stimulator (Nb. clinical signs may precede twitches due to different sensitivities to NMBD between muscle groups – See below)

When infusion a ND NMBD, keep the rate at or just above the rate that allows some return of neuromuscular transmission

- Characteristics of ND neuromuscular block:
 - Clinical – Lack of skeletal muscle fasciculation at onset of NMJ blockade
 - Peripheral nerve stimulation:
 - (i) Decreased twitch response to single stimulus
 - (ii) Tetanic fade present (unsustained response during continuous stimulation or tetany)
 - (iii) Fade present with TOF (TOFR < 0.7) and DBS
 - (iv) Presence of posttetanic potentiation
 - (v) Potentiation of block by other ND NMBD
 - (vi) Block antagonism by AChEi
- Reversal of a ND neuromuscular block occurs via either:
 - (i) Spontaneous reversal – The agent gradually diffuses away from the MEP, and is metabolised and excreted
 - (ii) Pharmacological reversal – Administer AChEi (reversal agent), which indirectly re-establishes normal nicotinic neuromuscular transmission. It binds to AChE and reversibly inactivates it. This prevents hydrolysis of ACh, which leads to a rise in synaptic content of ACh that can compete with the muscle relaxant for the nAChR

Causes of Altered ND NMBD Responses:

Pharmacological factors:

Drug	Clinical effect	Mechanism
Volatile agents	- Dose-dependent enhancement of ND NMBD effect and duration - Reduce ND NMBD dose by > 15% - Desflurane > Sevoflurane > Isoflurane > Halothane > N ₂ O	- ↓ skeletal muscle tone 2° CNS depression - ↓ postjunctional NMJ membrane sensitivity to depolarisation - ↑ NMBD delivery to NMJ 2° ↑ skeletal blood flow
ND NMBD	- Combination with other ND NMBD (esp from other group – aminosteroid vs benzylisoquinoline) produce synergistic effect	- Different NMBD structure permits synergistic antagonism of postjunctional nAChR
	- Use of priming dose enhances onset of NMB	- Blocks spare receptors
SCh	- Effect of ND NMBD enhanced following SCh at 1 mg/kg IV (even when SCh effects subsided)	- Postjunctional membrane remains desensitised by SCh → Prolongs effects of ND NMBD
Antibiotics	- Esp aminoglycosides (but also tetracyclines and polymyxins) enhance NMBD effect	- Stabilises prejunctional membrane – Competes with Ca ²⁺ → Attenuates presynaptic ACh release
Local anaesthetics	- Small doses enhance NMBD effect	- Interferes with prejunctional ACh release

(and anti-arrhythmics)	- Large doses can directly inhibit NMJ transmission	- Stabilises postjunctional membrane - Directly depress skeletal muscle fibre activity
Diuretics	- At 1 mg/kg – Enhances NMB effect	- Prejunctional effect – Inhibits cAMP production → Decreased presynaptic ACh release
	- At extreme doses – Antagonises NMB effect	- Prejunctional effect – Inhibits PDE → Increased cAMP levels → Increased ACh release
Lithium	- Enhance NMB effect	- Inhibition of VG Na ⁺ channels
Immunosuppressants	- Azathioprine antagonises NMB effect	- Prejunctional effect – Inhibits PDE → Increased cAMP levels → Increased ACh release
	- Cyclosporine – Enhances NMB effect	Unknown
Anticonvulsants	- Phenytoin/carbamazepine antagonise NMB effect	- Increased metabolic enzyme synthesis → Increased clearance of NMBD
Magnesium	- Increased NMB effect	- Prejunctional effect – Competes with Ca ²⁺ → Decreased presynaptic ACh release - Postjunctional effect – Decreased nAChR sensitivity to ACh
Drugs affecting SNS	- Ephedrine facilitates onset of NMBD	- Due to increased blood flow to NMJ
	- Beta-blockers delay onset of NMBD	- Due to decreased blood flow to NMJ
	- CCBs prolong NMBD effect	- Less prejunctional Ca ²⁺ → Inhibits presynaptic ACh release
Dantrolene	- Enhances NMBD effect	- Direct skeletal muscle relaxant
4-aminopyridine	- Antagonises effect of ND NMBD - Used to treat LEMs and MS	- K ⁺ channel blocker → Prolongs nerve AP → Increased presynaptic ACh release

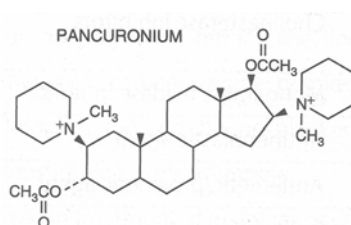
Physiological factors:

Factor	Clinical effect	Mechanism
Hypothermia	- Prolongs NMBD effect	- Due to reduced drug metabolism (esp atracurium/cisatracurium), hepatic enzyme activity, biliary/renal clearance, and clearance from NMJ
Acidosis	- Prolongs NMBD effect	- Impairs metabolism and clearance of drug - Antagonises reversal agent effect
Potassium level	- Hypokalaemia increases sensitivity to ND NMBD, but antagonises SCh	- Due to hyperpolarisation of postjunctional membrane
	- Hyperkalaemia increases sensitivity to SCh, but antagonises ND NMBD	- Due to depolarisation of postjunctional membrane
Hypocalcaemia	- Prolongs effect of NMBD	- Less prejunctional Ca ²⁺ → Less presynaptic ACh release
Burns injury (> 30%)	- Resistance to effect of ND NMBD	- Due to altered affinity of extrajunctional nAChR to drug
Denervation injury (Eg. post-CVA)	- Resistance to effect of ND NMBD	- Due to altered affinity of extrajunctional nAChR to drug
Gender	- Women more sensitive to NMBD than men	- Due to smaller % skeletal muscle mass

Long-Acting ND NMBD: Pancuronium

- Structure and preparation:

- Structure – Bisquaternary aminosteroid ND NMBD



- Preparation – Clear colourless solution of pancuronium bromide (4 mg in 2 mL; 2 mg/mL) that is stored at 4°C (or at room temperature for 6 months only)
- Dose, onset and duration of action:

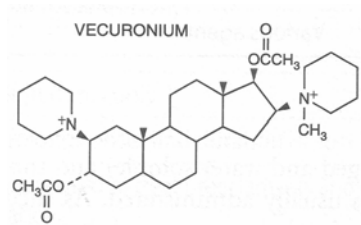
ED₉₅ of pancuronium: 0.07 mg/kg
- Intubating dose of 0.05-0.1 mg/kg IV – Intermediate onset in 90-150 secs with prolonged duration of action of 60-90 mins. Mean recovery index of 16-22 mins
- Subsequent doses are 1/3rd intubating dose (0.04 mg/kg) every 20-40 mins
- Pharmacokinetics:
 - 20-60% protein-bound (mainly albumin/gamma-globulin)
 - Vd 0.27 L/kg
 - Clearance 1.5-2.2 mL/min/kg and t_{1/2} β 70-130 mins
 - 40% undergoes hepatic metabolism – Deacetylation to 3-desacetyl-, 17-desacetyl-, and 3,17-desacetyl-pancuronium; 3-desacetyl-pancuronium is an active metabolite (50%), while others have minimal activity
 - Remainder is eliminated unchanged in urine (80%) and bile (20%)
 - Note – Dose adjustment required with hepatic/renal failure due to risk of prolonged duration of action
- Clinical effects:
 - (i) CVS effects
 - 10-15% increase in HR, MAP and CO (but no change in SVR) – An issue in patients at risk of cardiac arrhythmias and/or myocardial ischaemia
 - Cause by selective cardiac vagal blockade in SA node (mAChR) and sympathomimetic effect (SNS ganglion stimulation, enhanced NAd release from Adr nerve endings, and blockade of NAd reuptake into post-ganglionic Adr nerve endings)
 - (ii) Histamine release (causing bronchospasm, skin flushing, hypotension due to peripheral vasodilation) is very rare
 - (iii) Rarely cause anaphylaxis/anaphylactoid reactions
 - (iv) Can be reversed by sugammadex (but less effective than rocuronium and vecuronium)
 - (v) Critical illness myopathy

Aside: Critical illness myopathy

- Skeletal muscle weakness on recovery that generally occurs in critically ill patients with MOF that have required prolonged drug-induced skeletal muscle paralysis to facilitate mechanical ventilation
- Associated with use of aminosteroid ND NMBDs (esp pancuronium and vecuronium) but also atracurium. Pre-treatment with steroids further increases the risk
- Mechanism of prolonged NMB – Reduced drug clearance (due to renal/liver dysfunction) or presence of active metabolites of NMBs
- Prevented by close monitoring of NMBD infusions

Intermediate-Acting ND NMBD: Vecuronium

- Structure and preparation:
 - Structure:
 - Monoquaternary aminosteroid ND NMBD that is basically pancuronium WITHOUT a quaternary methyl group in A-ring of the steroid nucleus
 - Consequences – (i) Less ACh-like features (esp 20x less vagolytic tendency), and (ii) More lipid soluble (more uptake in liver and bile)



- Preparation:
 - Unstable in solution and thus stored as a lyophilised powder (containing mannitol and NaOH or citrate phosphate buffer)
 - Two vials (4 mg per vial) need to be dissolved in water (2 mL per vial) to form a clear colourless solution (2 mg/mL)
- Dose, onset and duration of action:

ED₉₅ of vecuronium: 0.05 mg/kg IV

- Intubating dose of 0.08-0.1 mg/kg IV – Intermediate onset in 90-120 secs and medium duration of action (20-35 mins). Mean recovery index of 15-30 mins
- Subsequent doses are 1/3rd of intubating dose (0.04 mg/kg IV) every 15-20 mins
- Can be given as an infusion at 50-80 µg/kg/hr, titrated to effect
- Pharmacokinetics:
 - 60-90% protein bound
 - Vd 0.18-0.27 L/kg
 - Clearance 3-6 mL/kg/min and t_{1/2} β 30-80 mins:
 - Hepatic metabolism (55%) – Deacetylated to 3-desacetyl-, 17-desacetyl-, and 3,17-desacetyl-vecuronium. 3-desacetyl-vecuronium has 50% potency as parent compound but is rapidly converted to 3,17-desacetyl-vecuronium (unlike pancuronium which is slower). 17- and 3,17-metabolites are minimally active (10% potency as parent compound)

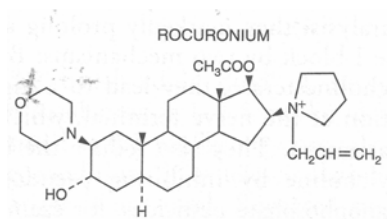
Aside: Pancuronium and vecuronium share similar clearance mechanisms, BUT the duration of vecuronium is shorter because – (i) It is extensively taken up by the liver due to its high lipid solubility, and (ii) Its active metabolite (3-desacetyl-vecuronium) is metabolised faster than pancuronium's active metabolite (3-desacetyl-pancuronium)

- Remainder undergoes renal excretion unchanged (25%) and biliary excretion unchanged (20%)
- Note – Dose adjustment required with hepatic/renal failure and cholestasis due to risk of prolonged duration of action
- Clinical effects:
 - (i) Nil CVS effects due to (a) lack of vagolytic effects, and (b) lack of histamine release – This raises an issue of bradycardia 2° to vagotonic procedures (esp laparoscopy, eye cases) or anaesthetic agents (esp propofol, fentanyl)
 - (ii) Nil histamine release (thus no bronchospasm, skin flushing, hypotension due to peripheral vasodilation)
 - (iii) Anaphylactoid/anaphylaxis is rare (lower risk than rocuronium)
 - (iv) Can be reversed by sugammadex (but less effective than rocuronium)
 - (v) Critical illness myopathy (See above)
 - (vi) Precipitates with thiopentone (I.e. blocks IVC), thus IV line needs to be flushed after thiopentone is given

Intermediate-Acting ND NMBD: Rocuronium

- Structure and preparation:

- Structure – Monoquaternary aminosteroid ND NMBD that is derived from vecuronium (similar structure EXCEPT for hydroxyl group (instead of acetyl group) on A-ring of steroid nucleus)



- Preparation – Clear and colourless solution as rocuronium bromide (50 mg in 5 mL; 10 mg/mL)
- Dose, onset and duration of action:

ED₉₅ of rocuronium: 0.3 mg/kg IV

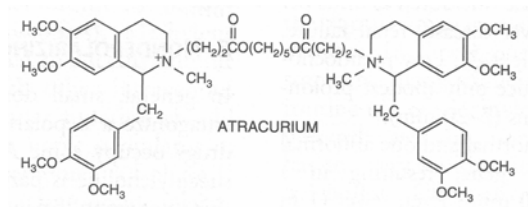
- Intubating dose 0.6 mg/kg IV – Intermediate onset in 100-120 secs with medium duration of action of 20-35 minutes. Mean recovery index of 8-17 minutes
- Subsequent doses are 25% of the intubating dose (0.15 mg/kg) every 30-40 mins
- Can be given as an infusion at 5-12 µg/kg/hr, titrated to effect
- Modified RSI dose 0.9-1.2 mg/kg IV (3-4x ED₉₅) can produce intubating conditions in 60 secs (similar to Sch 1 mg/kg IV) BUT there is issues of prolonged block at higher doses (unless sugammadex is used)

Note – Rocuronium is the ONLY ND NMBD that can be used as an alternate to Sch for rapid onset NMB as part of RSI due to its lack of potency (Ie. higher dose allows more agent to diffuse into NMJ from plasma)

- Pharmacokinetics:
 - 30% protein bound
 - Vd 0.27 L/kg
 - Clearance 3.9 mL/kg/min and t_{1/2} β 97 mins:
 - Hepatic uptake and excretion in bile unchanged (60%)
 - Renal excretion unchanged (40%)
 - Does NOT undergo any metabolism
 - Note – Its effects can be prolonged in hepatic/renal failure
- Clinical effects:
 - (i) Minimal CV effects – Mild vagolytic effect with slight rise in HR and MAP (this is useful against bradycardia 2° vagotonic procedures (esp laparoscopy, eye cases) or certain anaesthetic agents (esp propofol, fentanyl))
 - (ii) Nil histamine release (thus no bronchospasm, skin flushing, hypotension due to peripheral vasodilation)
 - (iii) Fatal anaphylactoid/anaphylaxis reaction more common (second to Sch)
 - (iv) Can be reversed by sugammadex at ANY time
 - (v) Used as precurarisation with 0.1 mg/kg 2-3 minutes prior to induction – Can be with either (i) Rocuronium (produces faster onset of relaxation), or (ii) Sch (decreases fasciculation, raised IAP/ICP/IGT, cardiac effects, and postoperative myalgia; this relaxes the LOS and increases aspiration risk)
 - (vi) Precipitates with thiopentone (Ie. blocks IVC), thus IV line needs to be flushed after thiopentone is given

Intermediate-Acting ND NMBD: Atracurium

- Structure and preparation:
 - Structure – Bisquaternary benzyliisoquinolinium ND NMBD that consists of a mixture of 10 stereoisomers due to 4 chiral centres (Nb – 15% is Cis-atracurium)



- Preparation:
 - Clear colourless solution with 10 mg/mL of atracurium besylate (2.5, 5, 25 mL vials) that must be stored at 4°C
 - Iodide besylate salt permits water solubility and adjusts pH at 3.25-3.65
 - Atracurium is stable at pH 4 and at 4°C only (Nb. at room temperature, it must be used within 14 days as 5-10% potency is lost each month)
- Dose, onset and duration of action:

ED₉₅ of atracurium: 0.2 mg/kg IV

- Intubating dose of 0.3-0.6 mg/kg IV – Slow onset of 3-5 minutes and medium duration of action of 20-35 minutes. Mean recovery index of 10-16 mins
- Subsequent doses 1/3rd of intubating dose (0.25 mg/kg) every 10-20 mins
- Can be given as an infusion at 5-10 µg/kg/min, titrated to effect
- Pharmacokinetics:
 - 80% protein-bound
 - Vd 0.15 L/kg
 - Clearance 5-6 mL/kg/min and t_{1/2} β 17-20 mins:
 - (i) Non-specific plasma esterases (60%)
 - Ester hydrolysis of atracurium into inactive metabolites (quaternary alcohol, acid and laudanosine)
 - Metabolism accelerated by acidosis, and slowed by alkalosis
 - (ii) Hofmann elimination (40%)
 - Nonenzymatic degradation at physiological body temperature and pH into inactive metabolites (laudanosine and quaternary monoacrylate)
 - Elimination accelerated by alkalosis and hyperthermia, and slowed by acidosis and hypothermia
 - Nb – Both pathways are independent of hepatic/renal function and PC activity, and can be used in renal/hepatic dysfunction or with atypical PC

Aside: Laudanosine

- Laudanosine is major metabolite of BOTH pathways – 2x molecules formed via Hofmann elimination, 1x molecule formed via non-specific plasma esterase pathway
- Inactive at NMJ, but at high [] it is a CNS stimulant (as a glycine antagonist) – It causes seizures (epileptic spikes on EEG) and raises MAC of volatile agents
- However, these effects are seen only at (i) excessively high doses in lab animals not used clinically, or (ii) Liver/renal failure and cholestasis (as it is metabolised by the liver, and excreted via bile/urine)

- Clinical effects:
 - (i) CVS effects – Tachycardia and hypotension when high doses given (> 0.5 mg/kg IV) due to histamine release and non-histamine mechanism
 - (ii) Dose-dependent release of histamine (especially if > 0.5 mg/kg) causing bronchospasm, skin flushing, hypotension due to peripheral vasodilation
 - (iii) Allergic reactions

- Anaphylactoid reactions are rare (due to acrylate-mediated immune activation or direct immunogenicity)
- Anaphylaxis can occur due to IgE-mediated reactions against substituted ammonium compounds, or previous sensitisation to acrylate (generally in haemodialysis patients)
- (iv) Possible laudanosine toxicity
- (v) Myopathy due to critical illness myopathy
- (vi) Sensitivity to pH/temperature – Prolonged duration of action if patient is acidotic or hypothermic
- (vii) Chemical incompatibility – Precipitates as free acid if mixed with alkaline solution (Eg. thiopentone) in an IV line

Intermediate-Acting ND NMBD: Cisatracurium

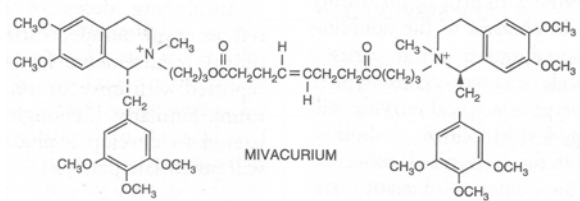
- Structure and preparation:
 - Structure – Bisquaternary benzylisoquinolinium ND NMBD that is a purified form of one of the ten stereoisomers of atracurium
 - Preparation – Clear colourless solution of cisatracurium besylate (10 mg in 5 mL; 2 mg/mL) that must be stored at 4°C. Iodide besylate salt permits water solubility and adjusts pH at 3.25-3.65. It is stable at pH 4 and at 4°C only (Nb. at room temperature, it must be used within 14 days)
- Dose, onset and duration of action:

ED₉₅ of cisatracurium: 50 ug/kg IV

 - Intubating dose of 0.1-0.15 mg/kg IV – Slow onset of 3-5 minutes and medium duration of action of 20-35 minutes. Mean recovery index of 10-16 mins
 - Subsequent doses 1/3rd of intubating dose (0.03 mg/kg) every 20-25 mins
 - Can be given as an infusion at 1-2 µg/kg/min, titrated to effect
- Pharmacokinetics:
 - 80% protein-bound
 - Vd 0.15 L/kg
 - Clearance:
 - Hofmann elimination (77%; See above) – Note that since less drug dose is given (due to greater potency of cisatracurium), less metabolites (esp laudanosine) are produced
 - Renal clearance (16%)
 - Nb – Nonspecific esterases are NOT involved (cf. atracurium)
 - Nb – Both pathways are independent of hepatic/renal function and PC activity, and can be used in renal/hepatic dysfunction or with atypical PC
- Clinical effects are similar to atracurium EXCEPT:
 - (i) Lower drug doses are given (due to 3-4 X more potency), BUT this means BUT slower onset (as less drug in plasma that can diffuse in NMJ)
 - (ii) Laudanosine toxicity is less common (likely due to lower doses used)
 - (iii) Does not produce a dose-dependent histamine release, thus no CVS effects (such as tachycardia and hypotension)
 - (iv) Hardly any anaphylaxis/anaphylactoid reactions

Short-Acting ND NMBD: Mivacurium

- Structure and preparation:
 - Structure – Bisquaternary ammonium benzylisoquinolinium ND NMBD that consists of 3 stereoisomers:
 - Trans-trans (58%) and Cis-trans (36%) isomers are active and equipotent
 - Cis-cis isomer (6%) have 10% activity (cf. other isomers)



- Preparation – Clear, pale-yellow aqueous solution of mivacurium chloride (2 mg/mL) in 5 and 10 mL ampoules. Acidic solution pH 3.5-5 and can be stored at room temperature for 18 months
- Dose, onset and duration of action:

ED₉₅ of mivacurium: 0.08 mg/kg IV

- Intubating dose of 0.07-0.15 mg/kg IV – Intermediate onset of 2-3 mins, and short duration of action of 12-30 mins (2x longer than SCh, but 30-50% shorter than intermediate-acting ND NMBD). Mean recovery index of 6.6 mins
- NMB can be maintained by either intermittent boluses of 0.1 mg/kg IV every 15 minutes OR an infusion at 4-10 µg/kg/min, titrated to effect
- Pharmacokinetics:
 - 10% protein-bound
 - Vd 0.1-0.3 L/kg (depending on isomer)
 - Clearance 50-90 mL/kg/min and t_{1/2} β 2.1-2.3 mins (depending on isomer):
 - Majority undergo metabolism (90%):
 - Trans-trans and cis-trans isomers hydrolysed by plasma cholinesterase (at 88% rate that of SCh) into inactive metabolites (quaternary amino alcohols and monoesters)

Note:

- Mivacurium's short duration of action is due to rapid hydrolysis by plasma cholinesterase
- Similar issues with prolonged NMB occur with genetically-aberrant PC (Ea/Ea causes paralysis for hours; Eu/Ea causes 2x block duration) and altered PC function 2° to disease states (Eg. renal, hepatic, cardiac failure; burns; Etc.) and medications (Eg. pancuronium, AChEi, Etc.)

- Cis-cis isomer undergoes metabolism by liver esterases into minimally active metabolites
 - Biliary and renal excretion unchanged is minor (10%)
- Clinical effects:
 - (i) Recovery from NMB 2° mivacurium
 - Rapid spontaneous recovery due to metabolism by plasma cholinesterase may not necessitate use of a reversal agent
 - AChEi readily reverses mivacurium-induced NMB BUT there is an issue of attenuating PC activity (thus interfering with normal spontaneous recovery) – Therefore, edrophonium should be used in favour of neostigmine as it does not inhibit PC function
 - (ii) CVS effects (tachycardia and hypotension) occur at doses > 2x ED₉₅ due to histamine release
 - (iii) Histamine release (similar to atracurium) causes bronchospasm, skin flushing, hypotension due to peripheral vasodilation
 - (iv) Fatal anaphylactoid/anaphylaxis reactions are rare
 - (v) Issues with prolonged NMB 2° dysfunctional plasma cholinesterase
 - (vi) Chemical incompatibility – Precipitates as free acid if mixed with alkaline solution (Eg. thiopentone) in an IV line

(e) *To describe and evaluate different methods of monitoring neuromuscular junction.*

Overview of a peripheral nerve stimulator:

- Peripheral nerve stimulator is used to assess the type and magnitude of NMJ blockade caused by neuromuscular blocking agents, which can then allow interpretation of the rate of onset/offset of muscle relaxation and duration of NMJ blockade
- Its use is indicated when:
 - (i) An intermediate- or long-acting NMJ blocker is used
 - (ii) A continuous infusion of short-acting NMJ blocker is used
 - (iii) To assess paralysis following RSI

Process of peripheral nerve stimulation:

- (1) As NMJ function is being measured (and not muscle function), ECG pads are applied over a peripheral motor nerve (usually the ulnar nerve or facial nerve) and not the muscle

Note:

- Any peripheral motor nerve can be used so long as (i) it is close to the skin to be stimulated, and (ii) muscle contraction is visible or palpable to allow measurement of the evoked response
- Good electrical contact with skin is required (I.e. clean skin with alcohol rub)
- -ve electrode (black) is applied over the most superficial part of nerve distally, while the +ve electrode (red) is applied proximally along the course of the nerve

- (2) Each electrical stimulus applied is of a monophasic square-wave pattern (which allows a constant current to be maintained throughout the stimulus), 0.2 msec duration and supramaximal current intensity. The frequency of stimulation patterns will vary depending on analysis required (Eg. TOF, DBS, PTC/F, tetany, single twitch)

Note:

- To produce maximal muscle contraction with each electrical stimulus, ALL motor nerve fibres in the peripheral nerve need to be stimulated to generate an AP. This requires delivery of an electrical current of sufficient:
 - (i) Magnitude – Supramaximal stimulus (60-80 mA) must be delivered. This is 25% above “Maximal stimulus”, which is current that causes all nerve fibres to depolarise
 - (ii) Duration – A constant supramaximal stimulus must be applied for an adequate duration (0.1-0.3 msec). This is achieved using a monophasic square-wave pattern of 0.2 msec
- Thus, an ideal peripheral nerve stimulator should be able to deliver electrical stimuli of:
 - (i) A constant current up to 80 mA (rather than a constant voltage) – This is because (a) current that determines nerve depolarisation, and (b) skin resistance is variable and causes current to vary when a fixed voltage is delivered (I.e. risk of inframaximal stimulus)
 - (ii) Monophasic square-wave type of 0.1-0.3 msec duration

- (3) An evoked mechanical response in the target muscle of the stimulated nerve (adductor pollicis for ulnar nerve; orbicularis oculi for facial nerve) is measured either (i) Subjectively (by visual and/or tactile means), or (ii) Objectively (by acceleromyography, electromyography, mechanomyograph)

Using peripheral nerve stimulation during anaesthesia:

- Muscle relaxation will vary at different muscle groups such that when a NMBD is administered, a “Paralytic march” is described in textbooks in the following order with onset, and in the reverse order with recovery:

Extrinsic eye muscles → Small facial muscles → Limbs → UAW and Larynx → Respiratory muscles

- However, clinically when a NMBD is given the onset/offset of muscle groups follow a different pattern:
 - o (i) Central muscles (diaphragm, intercostal, larynx, facial/eye muscles) have the fastest onset and offset (mainly due to good regional blood flow)
 - o (ii) Peripheral muscle (adductor pollicis) have the slowest onset and offset (mainly due to poor regional blood flow)
 - o (iii) UAW muscles (Eg. pharynx) have fast onset similar to central muscles BUT slower offset similar to peripheral muscles (mainly due to sensitivity to NMBD)

In summary:

- Onset: Larynx, Facial/Eye, UAW muscles → Respiratory muscles → Adductor pollicis
- Offset: Respiratory muscles → Larynx, Facial/Eye, UAW muscles → Adductor pollicis

- The reasons for the varying onset/offset in different muscle groups are due to:
 - o (i) Differences in regional blood flow (Ie. more to central muscles)
 - o (ii) Muscle size, fibre/twitch type, and innervation
 - o (iii) Muscle temperature (Ie. cooler in peripheries)
 - o (iv) Differences in dose requirements (facial muscle, diaphragm, jaw and larynx/glottic muscles have a higher ED₉₅ for relaxation than the adductor pollicis, such that the dose of NMBD to block the diaphragm is twice that to produce similar effect at adductor pollicis)
- This has important implications for peripheral nerve stimulator monitoring during anaesthesia:
 - o (1) Monitoring during induction:
 - Orbicularis oculi should be monitored for onset of NMB – This is because the degree of its NMB accurately mirrors the paralysis central muscles (esp larynx, diaphragm and jaw) required for tracheal intubation
 - Adductor pollicis is a poor monitor as it can provide a false reassurance of paralysis – This is because when it is maximally relaxed, the central muscles will have already done so and the relaxant effect is likely waning
 - Monitoring is best done with single twitch or TOF count (Ie. loss of TOFC or single twitch indicates ideal intubating conditions)
 - o (2) Monitoring during maintenance:
 - Orbicularis oculi should be monitored for maintenance of NMB – This is because it shares similar resistance to NMBD as the central muscles (esp respiratory muscles).
 - Adductor pollicis is a poor monitor as it is more sensitive to the effects of NMBD and can underestimate the level of respiratory muscle paralysis
 - Monitoring of deep relaxation is best done with TOF count and PTC
 - o (3) Monitoring during reversal/recovery:
 - Adductor pollicis should be monitored for offset of NMB – This is because its offset is slower than the central muscles. This provides a large safety of margin as when adductor pollicis fully recovers, the respiratory, laryngeal and UAW muscles will have already long recovered
 - Monitoring is best done with TOF (count/ratio), DBS or tetany

Patterns of peripheral nerve stimulation:

- (1) Single twitch stimulation
 - o Defined as a single 0.2 msec stimulus applied every 1 to 10 secs (1-0.1 Hz)

Receptor occupancy	Effect on single twitch
75%	Single twitch height begins to reduce
85%	Single twitch height 50%
90%	Single twitch height 25%

95%	Loss of single twitch
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- Clinical use – Useful in establishing level at which supramaximal stimulus is obtained, and to assess onset of NMB
- Limitations of use – Requires baseline twitch height pre-induction for meaningful interpretation. Uncomfortable and grossly insensitive indicator of recovery
- (2) Tetanic stimulation
 - “Tetany” is achieved when individual stimuli applied at > 30 Hz frequency causes muscle twitches to fuse into a sustained muscle contraction
 - “Tetanic stimulation” is defined as sustained high-frequency stimuli at 50-100 Hz for 5 secs
 - Normal evoked stimulus – Tetanic contraction maintained at maximal intensity; however, at > 100 Hz, muscle fatigue can occur leading to fade
 - Phase 1 depolarising NMB – Tetanic contraction maintained without fatigue or fade, but of reduced intensity
 - Non-depolarising NMB or Phase 2 depolarising NMB
 - Gradual diminution of evoked muscle contraction responses is seen (fade)
 - Clinically it is the most sensitive (and reliable) monitor of minor degrees of NMB (receptor occupancy of 50% when fade absent at 100 Hz; 70% at 50 Hz) BUT limited by severe pain!
- (3) Post-tetanic potentiation (or facilitation) and count
 - PTP/PTF is defined as an augmented evoked single twitch response that occurs 3 seconds after a 5 seconds 50 Hz tetanic stimulus – This is present only with non-depolarising NMB or phase 2 depolarising NMB, and in the absence of any NMB. It is absent in the presence of a phase 1 depolarising NMB
 - PTC is defined as the number of evoked single twitch responses counted in response to single twitch stimuli repeated at 1 Hz 3 seconds after a 5 second of 50 Hz tetany – This is used clinically to assess the depth of an intense NMB (Ie. no single twitch or TOFC) where receptor occupancy is > 95%. The PTC is inversely related to depth of block (or when T1 of TOF will reappear), such that T1 reappears when PTC is 8-10
 - Nb – Effects of tetanic stimulation lasts up to 6 minutes, thus PTC/PTP should NOT be repeated in this time as the depth of NMB will be underestimated!
- (4) Train of four (TOF)
 - Defined as a series of four 0.2 msec single twitch stimuli delivered over 2 seconds (2 Hz), with 0.5 sec separating each stimulus
 - Allows assessment of – (i) TOF ratio (ratio of 4th twitch height to 1st twitch height (T4:T1)), and (ii) TOF count (number of twitches)
 - TOF findings:
 - Normal evoked stimulus – TOF ratio 1 (no fade), TOF count 4, and maximal twitch amplitude
 - Phase 1 depolarising NMB – TOF ratio 1 (no fade), TOF count 4, but decreased twitch amplitude
 - Non-depolarising NMB or Phase 2 depolarising NMB
 - With increasing block, there is initially (i) reduction in twitch height amplitude (T4 affected first, then T3, then T2, then T1) to produce “Fade”, then with greater block intensity, (ii) reduction in twitch count (T4 disappears first, then T3, then T2, then T1). With recovering block, the reverse order occurs

Receptor occupancy	Effect on TOF
> 70%	T4 starts to decrease in size
70-75%	T3 and T2 start to decrease in size

75-80%	T1 starts to decrease in size (associated with T4 height depression of 75%)
85-90%	T4 disappears (associated with T1 height depression of 75%)
90-95%	T3 and T2 disappear (associated with T1 height depression of 80-90%)
> 95%	T1 disappears

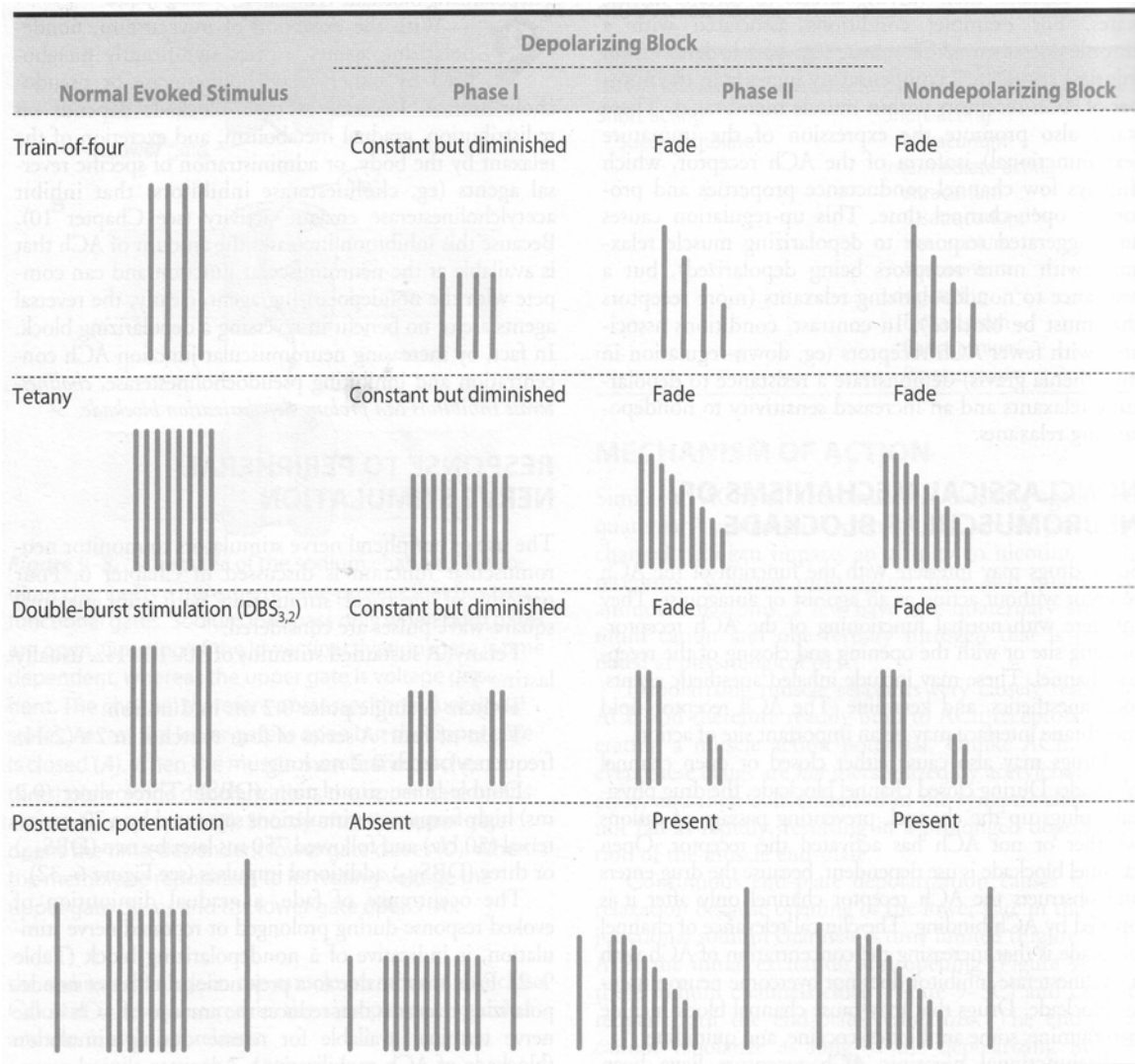
- Clinical relevance:
 - (i) TOF count correlates with the depth of NMB (such that reversal agents can be given at TOFC > 2)
 - (ii) TOF ratio correlates with recovery from NMB (such that TOFR > 0.7 reflects adequate reversal to permit spontaneous ventilation, and TOFR > 0.9 suggests adequate reversal to permit extubation)
- (5) Double-burst stimulation (DBS)
 - Defined as two short bursts of 50 Hz tetany separated by 750 msec, with each burst consisting of three 0.2 msec stimuli (each separated by 20 msec interval)
 - DBS findings:
 - Normal evoked stimulus – Two evoked muscle contractions of equal and maximal intensity
 - Phase 1 depolarising NMB – Two evoked muscle contractions of equal but decreased intensity
 - Non-depolarising NMB or Phase 2 depolarising NMB
 - Evoked muscle contractions will have reduced intensity, but this is more prominent in the second evoked muscle contraction (fade)
 - Clinical relevance – More sensitive than TOFR in detecting small amounts of residual NMJ blockade such that when the magnitude of both evoked contractions are equal, then clinically significant residual NMJ blockade does not exist (Nb. this occurs at 60-70% receptor occupancy). Use limited by pain when patient is awake

Response to peripheral nerve stimulation: Depolarising and Non-depolarising blocks

- Non-depolarising blocks and phase 2 blocks of depolarising agents produce:
 - (i) Fade with TOF, tetany and DBS – Gradual diminution of evoked responses during prolonged or repeated nerve stimulation

Mechanism of fade – Due to a prejunctional effect Inhibition of presynaptic nAChR receptors results in loss of a +ve feedback loop that further mobilises presynaptic ACh at times of peak activity
 - (ii) Posttetanic potentiation – Tetanic stimulation causes an increased evoked response to a subsequent twitch

Mechanism of PTP – Due to transient increased synthesis and mobilisation of ACh or presence of Ca^{2+} in nerve terminal following completion of tetany
- Phase 1 blocks of depolarising agents demonstrate:
 - (i) Lack of fade with TOF, tetany and DBS. Instead, they display a constant but diminished evoke responses
 - (ii) Absence of posttetanic potentiation



Clinical assessment of neuromuscular blockade:

Clinical test	Suggestion of normal NMJ function	Receptor occupancy rate (for ND NMBD) when normal NMJ function is suggested	Advantages and disadvantages
Tidal volume	TV > 5 mL/kg	80%	Easy to assess via spirometry, but insensitive indicator of peripheral neuromuscular function
Vital capacity	VC > 20 mL/kg	70%	Easy to assess via spirometry and more sensitive than TV, but requires patient cooperation
Inspiratory force	P < -40 cmH ₂ O	50%	Easy to assess via spirometry and reliable gauge of normal diaphragmatic function
Head lift	Sustained > 5 secs	50%	Standard clinical test of normal NMJ function, but requires patient cooperation and supine positioning
Handgrip	Sustained level to preinduction baseline	50%	Sensitive of normal NMJ function, but requires patient cooperation and is a very subjective measure
Sustained bite	Sustained jaw clench	50%	Sensitive of normal NMJ function, but requires patient cooperation