HISTORY

- curare was used for many years by South American Indians as arrow poison
- West in 1932 used purified fractions of curare in patients with tetanus & spastic disorders
- used by Bennett in 1940 as an adjuvant to shock therapy

  **NB:** first used for muscle relaxation in anaesthesia in 1942 by Griffith and Johnson

- the structure was established by King in 1935, however, one of the nitrogen groups was later found to be tertiary
- a synthetic analogue, metocurine, was developed several years later with 3x the potency of dTC
- gallamine, another of the series, was synthesised about 1950

  **NB:** in 1954 Beecher & Todd published their multi-institutional report which showed a 6-fold increase in mortality with the use of muscle relaxants

- there were design faults with this study and Miller and other authors claim it was probably over-publicised
- however, at that time anticholinesterases were not in routine use for reversal of residual blockade and there was almost certainly a real increase in mortality associated with the use of neuromuscular blocking agents

- the study of the structure-activity relationship of the parent alkaloids led to the development of the polymethylene-bis-trimethylammonium series

- the antagonism of curare by anticholinesterase drugs was realised by Pal in Vienna in 1900
- the actions of succinylcholine were independently described in Italy, the UK and the USA around 1949
- discovery of its action was delayed many years as it had been used in experiments in conjunction with dTC

- introduction of other agents,
  1. alcuronium - 1961
  2. pancuronium - 1967
  3. fazadinium - 1972
  4. atracurium ~ 1980's
  5. vecuronium ~ 1980's
  6. rocuronium ~ 1990's
  7. mivacurium ~ 1990's

Neuromuscular Blockers
PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION

Anatomy of the Neuromuscular Junction

- as the motor neurone approaches the endplate it loses its myelin sheath and divides into a number of **terminal buttons**, or end feet
- **vesicles** are present in the terminal axoplasm, especially congregated near thick transverse bands of axonal membrane, or **active zones**
- the vesicles are synthesised in the cell body and travel to the terminals via microtubular transport
- there are ~ 1000 active zones and ~ 300,000 vesicles per nerve terminal
- the vesicles contain **acetylcholine**
- the terminal buttons fit into depressions in the motor endplate, which is a thickened portion of the muscle cell membrane
- beneath the nerve ending, the endplate membrane is thrown into a number of **palisades**
- the active zones are adjacent to the shoulders of the post-synaptic palisades, where ACh receptors are most densely populated
- the receptors themselves are organised into discrete **clusters**
- each cluster is ~ 0.1 µm in diameter, with the receptors anchored in pairs, in groups of several hundred, by the cytoskeleton
- they are absent from the valleys of the junctional folds and other parts of the muscle fibre surface
- at the crests the receptor density is ~ 5000 per µm², and there are millions of receptors per endplate
- at its narrowest the junctional gap is ~ 60 nm wide
- this is filled with so called "basement membrane", which is a collagen-like material rich in carbohydrate and containing most of the junctional **acetylcholinesterase**
- acetylcholinesterase molecules are also embedded in the post-junctional membrane, together with some on the nerve terminal
- only one nerve fibre supplies an endplate, there is no convergence, however, there may be considerable divergence → **innervation ratio**

- **Acetylcholine Receptor**
  - the nicotinic receptor of cells that are derived from the neural crest (**autonomic ganglia**), have a different pharmacological specificity to that of the neuromuscular junction
  - the receptor is a **pentamer**, composed of two α-subunits, each with a MW ~ 40,000 daltons, and three slightly larger subunits, β, δ, and ε
  - the **foetal receptor** possesses a γ-subunit in place of the epsilon, synthesis switching to the adult form in response to motor nerve innervation soon after birth
  - these subunits show partial homology of the AA sequence, therefore probably arise from a common **primordial gene**
  - all five subunits traverse the cell membrane and are arranged in a "**rosette**", with a central ion channel
only the *α*-subunits carry the recognition sequence for ACh
* the same sites bind reversible antagonists, such as dTC, and irreversible antagonists such as *α*-bungarotoxin
* both must be occupied for receptor activation and binding exhibits positive co-operativity, that
* this causes a conformational change in the receptor which allows the flux of small cations (Na⁺, K⁺, Ca++)
* patch clamp studies of human calf muscles have shown,
  a. mean channel opening ~ 6.6 ms
  b. current pulse ~ 3.5 pA
  c. single channel conductance ~ 30 pS (picoSiemens)
  d. δV across membrane ~ 50 mV

  a. an increase in the concentration of agonist increases the frequency of channel opening but does
  not alter the elementary event
  b. the duration of channel opening is dependent upon the type of agonist, open channel
  conductance remains constant
  c. measurement of the density of receptors and the conductance of the activated membrane reveal
  that the rates of ion translocation are sufficiently rapid, 5x10⁷ ions/sec, to require movement
  through an open channel
  d. further, the inward movement of Na⁺ & outward movement of K⁺ occur through a single class of
  channels

* a second class of cholinergic receptors appear to reside on the prejunctional membrane
* these receptors augment the release of ACh in response to nerve stimulation and are termed
  mobilisation receptors, R_mob
* there is also a third group, situated on the axon, at the nodes of Ranvier which are responsible
  for repetitive firing under certain conditions, R_rep

Mechanism of Transmission
* a propagated nerve action potential depolarises the nerve cell membrane →
  • increased nerve membrane gCa⁺⁺ (≡ cAMP & channel phosphorylation)
  • increased nerve [Ca⁺⁺] → calmodulin & synapsin I
  • marked increase in vesicle exocytosis with ACh release
  • ACh diffuses across the synaptic cleft to endplate ~ 60 nm
  • 2 x ACh combine with each specific ACh receptor
  • "activated" receptor increases membrane gNa⁺ & gK⁺
  • resultant influx of Na⁺ depolarises cell
  • endplate potential, produced → local current sink
  • activation of "voltage-gated" channels in surrounding muscle cell membrane
    → propagated muscle action potential
**Endplate Potential**

- the average motor endplate (MEP) contains ~ 50 million ACh receptors
- each nerve action potential releases ~ 60 vesicles @ 10,000 ACh molecules
- this is around 10 times the amount of ACh required to depolarise the MEP
- small amounts of ACh are released randomly from the resting nerve cell, each producing a minute depolarisation spike, or *miniature endplate potential*
  - the amplitude of these mepp’s ~ 0.5 mV
  - the number of quanta released varies,
    a. *directly* with the extracellular [Ca++]
    b. *inversely* with the extracellular [Mg++]

- addition of non-depolarising antagonist, eg. dTC, progressively diminishes the amplitude of the endplate potential
- this may fall to below 70% of its initial value before it fails to initiate a propagated muscle action potential → *safety factor* for conduction
- statistical analysis shows that dTC decreases the frequency of channel opening events, the duration and conductance remain constant
- the synaptic concentration of unbound ACh decays more rapidly than does the endplate potential, due to hydrolysis by membrane bound AChE
- data suggests that any one ACh molecule survives long enough to open only one channel
- *anticholinesterase* agents prolong the endplate potential by allowing successive rebinding of ACh molecules

**Structure-Activity Relationship**

- the natural transmitter, ACh, has a positively charged quaternary ammonium group which is attracted to the negatively charged receptor site
- the majority of non-depolarising agents have two such quaternary groups, with the exception of dTC which has only 1, and gallamine which is triquaternary
- this attraction of the quaternary ammonium group extends to other ACh receptors, ie.,
  a. *nicotinic receptors* in autonomic ganglia & adrenal
  b. *muscarinic receptors* at vagal nerve endings

- Bovet (1951) made a number of generalisations about the structure of these agents,
  a. the non-depolarising agents are bulky rigid molecules, c.f. the depolarising agents which tend to be flexible, enabling free bond rotation
  b. the interquaternary distance for the flexible depolarising agents may vary up to the maximal bond length (1.45nm for decamethonium), whereas the distance for the rigid non-depolarising agents is usually 1.2-1.4 nm
Neuromuscular Blockers

- the specificity of a compound for either the ganglionic, or the neuromuscular receptor is partly determined by the distance between the two positively charged groups
- for the polymethylene-bis-trimethylammonium, or "methonium" series,
  1. maximal **ganglionic** blockade occurs with 5-6 intervening CH₂ groups
  2. **neuromuscular** blockade is maximal with 10 groups

- thus, decamethonium is a depolarising muscle relaxant, while hexamethonium is a ganglionic blocking agent
- the tris-quaternary gallamine, the tertiary amine β-erythroidine and fasadinium are exceptions, the cationic charge being delocalized
- the importance of this has recently been questioned
- now generally believed that an interonium distance of 1.25 nm may confer optimal depolarising activity, however, this is **not critical** for non-depolarising blockade

- since 1964 these concepts have gradually lost importance, as
  a. alcuronium, pancuronium, and vecuronium having interonium distances of 1.0-1.1 nm
  b. dTC and gallamine not being bisquaternary
  c. fazadinium and atracurium having interonium distances of 0.75 and 1.8 nm respectively

- recent observations do allow a number of generalisations,
  a. an interonium distance of 0.8 nm promotes ganglionic blockade in the **steroidal bisquaternary**s, this effect being minimal between 1.0-1.8 nm (pancuronium, vecuronium, atracurium)
  b. **muscarinic** blockade predominates in trisquaternary structures
  c. muscarinic blockade in the steroidal bisquaternaries has been due to the ACh-like substitution on the A-ring, removal of the quaternary methyl group greatly reducing their ACh-like character and vagolytic properties (pancuronium → **vecuronium**)  
  d. **benzylisoquinoline** substances (dTC, metocurine, atracurium, mivacurium) release histamine, which is reduced by substitution of the methoxy groups
  e. removal of the acetoxy groups from vecuronium results in an agent of low potency, very rapid onset but marked M₂ affinity, Bowman et al concluding that a rapid **onset** agent will display **low affinity**

- in general, the bis-quaternary compounds do not possess strong ganglionic blocking or histamine releasing properties
- eg. methylation of dTC to metocurine increases neuromuscular potency but reduces the level of histamine release
- many other drugs, such as atropine, strychnine & quinine show a marked increase in potency when the N-group is quaternarised
QUANTIFICATION OF NEUROMUSCULAR BLOCKADE

- in 1958, Christie & Churchill-Davidson described assessment of neuromuscular blockade during anaesthesia by the use of a nerve stimulator
- neuromuscular function is monitored by evaluating the response of a muscle to supramaximal stimulation of a peripheral motor nerve,
  a. electrical stimulus ~ 20-25x > maximal response
  b. the impulse is monophasic & rectangular
  c. the optimal pulse duration ~ 0.2-0.3 ms
- a biphasic pulse may initiate a burst of action potentials and increase the response to stimulation
- a pulse duration > 0.5 ms may result in direct muscle stimulation, or initiate repetitive firing of the nerve
- pulse delivery should be at a constant current, cf. voltage, as stimulation is current dependent
- most commercially available stimulators only deliver a constant current over the range 25-50 mA, with a skin resistance ~ 2.5 kΩ
- this is a disadvantage, as with cooling the skin resistance may increase up to 5 kΩ and current delivery may be submaximal
- ideally the stimulator should have a high internal impedance and display the delivered current
- the ulnar nerve is commonly used and the adductor pollicis brevis observed by either,
  a. clinical assessment
  b. force transducer
  c. acceleration transducer
  d. compound-evoked electromyographic potential
- any readily accessible nerve may be used, eg. facial, lateral peroneal
- however, because different muscle groups have different sensitivities to neuromuscular blocking drugs, results from one group cannot necessarily be extrapolated to another
- the diaphragm is the most resistant, requiring ~ 1.4-2.0 times the concentration of neuromuscular blocker for a given degree of blockade than the adductor pollicis brevis
- also, the diaphragm exhibits a faster onset and faster recovery of neuromuscular blockade
- the source of these differences in unknown but may include,
  i. different safety margins for different groups
  ii. fibre composition
  iii. innervation ratio
  iv. blood flow
  v. muscle temperature
- the use of a less sensitive, peripheral muscle for administration has the advantage that overdosage is unlikely and upon peripheral recovery, recovery of the diaphragm is virtually complete
- an adverse point is, that even with no response to peripheral stimulation, complete paralysis of the diaphragm cannot be guaranteed
Patterns of Nerve Stimulation

- **Single-Twitch Stimulation** \( ST \)
  - single stimuli are applied at rates from 0.1 to 1.0 Hz
  - muscle response to single twitch stimulation depends upon the frequency of stimulation
  - at rates > 0.15 Hz, the evoked response will gradually decrease and settle at a lower level
  - therefore rates of \( 0.1-0.15 \text{ Hz} \) are generally used
  - accuracy is generally poor, as clinical assessment of twitch strength is usually employed and notoriously unreliable

- **Train of Four Stimulation** \( TOF \)
  - introduced by Ali et al. in 1970
  - four supramaximal stimuli are delivered at 2 Hz (1 per 0.5 sec)
  - each train is separated by 12-20 seconds
  - a TOF normally shows little difference between the four responses
  - the degree of competitive neuromuscular blockade may be assessed by,
    - the ratio of the \( 4^{th} \) to the \( 1^{st} \) response
    - the number, or TOF count
  - this enables assessment of transmission in the absence of baseline data
  - the patterns of response are,
    - normal → 4:1 ratio ~ 1.0
    - partial competitive blockade
      → the ratio decreases, or "fades", in relation to the degree of blockade
    - partial non-competitive blockade
      → the ratio remains ~ constant, twitch height uniformly reduced
  - the presence of TOF fade after the use of succinylcholine signifies the onset of phase II blockade
  - during recovery, once four responses can be elicited, it is difficult even for experienced observers to estimate the TOF ratio above ~ 0.4
  - accordingly, TOF is not useful for exclusion of residual neuromuscular paralysis
Assessment of TOF Responses

<table>
<thead>
<tr>
<th>Level</th>
<th>TOF</th>
<th>Ratio</th>
<th>Receptor Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intense Blockade</td>
<td>0/4</td>
<td>0</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>Moderate, or Surgical Blockade</td>
<td>1/4</td>
<td>0</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>2/4</td>
<td>0</td>
<td>85%</td>
</tr>
<tr>
<td>Recovery</td>
<td>3+/4</td>
<td>0</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>4/4</td>
<td>~ 0.2</td>
<td>75%</td>
</tr>
</tbody>
</table>

- **Tetanic Stimulation TS**
  - tetanic stimulation rates vary from 30, 50, 100 to 200 Hz
  - the usual pattern is 50 Hz for a period of 5 seconds
  - some recommend using high frequencies (100, 200 Hz) for 1 second
  - the patterns of response are,
    1. normal → no tetanic fade
    2. partial competitive blockade → tetanic fade
    3. partial non-competitive blockade → no tetanic fade
  - fade is believed to be due to depletion of readily available stores of ACh
  - at equilibrium, the rate of release is equal to the rate of mobilisation
  - in the absence of neuromuscular blockade, the muscle response is usually maintained due to the large safety factor for transmission
  - only when this safety factor is reduced by competitive postsynaptic blockade, does fade in the muscle response begin
  - in addition to blocking postsynaptic receptors, the nondepolarising neuromuscular blocking drugs also impair mobilisation of ACh within the nerve terminal
  - this effect may contribute to the fade seen both with tetanic stimulation and TOF stimulation
  - fade also depends upon the frequency and the duration of applied stimulation
  - the response to a single stimuli after a tetanic convulsion is normal, or slightly enhanced
  - during partial competitive block there is **post-tetanic facilitation** of transmission
  - this is believed to relate to the fact that increased mobilisation of ACh within the nerve continues for some time after tetanic stimulation
  - the degree and duration of PTF depend upon the degree of neuromuscular blockade
  - PTF usually disappearing within 60 seconds of tetanic stimulation
  - tetanic stimulation has a number of **disadvantages,**
    a. it is very **painful**
    b. in the late phase of recovery it may **prolonged blockade** in the muscle group tested
  - it is usually used to assess **residual** neuromuscular blockade
  - however, it offers **no** additional information to a TOF, unless combined with a post-tetanic count
  - if a 100Hz @ 5 sec tetanus is used there is an improvement in clinical assessment when compared to a TOF clinical assessment (MCQ - ? best method of assessment of residual blockade)
  - however, higher stimulation rates are considerably more painful

- Neuromuscular Blockers
Post-Tetanic Count PTC

- doses of neuromuscular blocking agents used to facilitate endotracheal intubation result in profound neuromuscular blockade
- assessment of this degree of blockade with ST or TOF is unsuccessful
- it is possible to quantify intense neuromuscular blockade by a post-tetanic count,
  1. single twitch, 1 Hz, for 1 minute
  2. tetanus, 5 seconds @ 50 Hz
  3. 3 seconds latency period
  4. single twitch count, 1 Hz, for 1 minute $\rightarrow$ count = ?/60

- after injection of an intubating dose, the reappearance of post-tetanic twitches begins prior to the first TOF response, by
  a. pancuronium ~ 35 mins
  b. atracurium ~ 7-8 mins
  c. vecuronium ~ 7-8 mins

- the main application is assessment of NMJ blockade when there is no response to ST or TOF
- it is also useful when any movement must be eliminated, such as in ophthalmic surgery
- to ensure total paralysis of the diaphragm, paralysis of peripheral muscles must be so intense that there is no response to PTC
- the response to PTC depends upon,
  a. the level of neuromuscular blockade
  b. the frequency & duration of tetanus
  c. the interval between the tetanus and stimulation
  d. the frequency of stimulation

- because of possible antagonism of neuromuscular blockade, localised to the tested muscle group, a PTC should not be performed more often than each 6 minutes

Double Burst Stimulation DBS

- developed with the specific aim of manual, or tactile, assessment of small amounts of residual neuromuscular blockade
- during late recovery from neuromuscular blockade, manual assessment of TOF responses is insufficient to exclude shallow degrees of residual blockade
- with DBS it is easier to "feel" fade in the response
- DBS consists of two short bursts of 50 Hz, separated by 750 ms
- the duration of each square wave in the burst is 0.2 ms
- initial studies were with 3 pulses @ 50 Hz in each burst, DBS$_{3,3}$
Double-Burst Stimulation  DBS\textsubscript{3,3}

- the normal response to DBS is two short muscle contractions of equal force
- in partially paralysed patients the second contraction is weaker
- measured mechanically, DBS correlates closely with the TOF response
- however, when measured manually, the assessment of DBS correlates more closely than manual TOF with the mechanical TOF response
- the absence of fade on DBS usually means significant residual neuromuscular blockade is absent

| Clinical Use of Modes of Electrical Nerve Stimulation |
|---------------------------------|------------------|--------------------|--------------------|
|                                 | During Induction | During Surgery     | Recovery           |
|                                 |                  |                    |                    |
|                                 | STP              | Supramax. Stimul'n  |                   |
|                                 |                  | Tracheal Intubation |                   |
|                                 |                  | Intense Blockade    |                   |
|                                 |                  | Moderate Blockade   |                   |
|                                 |                  | Reversal            |                   |
| ST                              | 1.0 Hz           | 0.1 Hz             | 50 Hz             |
| TS                              |                  |                    | 50 Hz             |
| TOF                             | 2 Hz             | 2 Hz               | 2 Hz              |
| PTC                             |                  |                    | ?                 |
| DBS                             |                  |                    |                   |
Conditions Warranting the Use of Peripheral Nerve Stimulation

1. where the pharmacokinetic profile will be abnormal,
   i. severe renal disease
   ii. liver disease
   iii. severe illness
   iv. extremes of age

2. where the pharmacodynamic profile will be abnormal,
   i. neuromuscular disease
   ii. drug interactions
   iii. burns
   iv. neonates

3. where spontaneous offset of blockade is undesirable
   i. ophthalmological procedures
   ii. neurosurgery
   iii. any microsurgical procedure

4. where maximal postoperative muscle power is required,
   i. severe pulmonary disease
   ii. myopathic & neuromuscular disorders
   iii. marked obesity
   iv. risk of aspiration

5. where pharmacological reversal of blockade is contraindicated, (?? ever)
   i. severe heart disease
   ii. severe bronchial asthma

6. prolonged procedures
   • where neuromuscular blockade is produced by continuous infusion
Patterns of Neuromuscular Blockade

1. **Nondepolarising Block**
   - the absence of muscle fasciculation
   - tetanic fade, with train of four (0.5-2 Hz)
   - post-tetanic potentiation
   - antagonism by anti-AChE agents
   - antagonism by depolarising relaxants
   - potentiation by nondepolarising relaxants

2. **Depolarising Block**
   - muscle fasciculations preceding paralysis
   - absence of tetanic fade at slow and fast rates
   - absence of post-tetanic potentiation
   - potentiation by anti-AChE agents
   - potentiation by depolarising relaxants
   - antagonism by nondepolarising relaxants

**Phase II or Dual Block**
- patients with normal plasma cholinesterase given a standard dose of succinylcholine will exhibit a usually phase I, or depolarising blockade
- phase II blockade occurs more commonly in patients either,
  a. given repeated doses of depolarising agents
  b. with atypical plasma cholinesterase activity
  c. with myasthenia gravis, or myasthenia-like syndromes
- typical depolarising blockade changes to one that exhibits many of the classical signs of competitive blockade
- clinically, phase II blockade in the presence of normal plasma cholinesterase activity may be reversed by neostigmine
- the effects of neostigmine in the presence of atypical plasma cholinesterase activity are unpredictable and may lead to intensification of blockade
- phase II block may be predisposed to by the inhalational anaesthetic agents
PHARMACOKINETICS

- most of these agents, possessing 1 to 3 ammonium groups, are,
  a. almost completely ionized at physiological pH
  b. highly water soluble
  c. only very slightly lipid soluble

- therefore, they tend to be,
  a. poorly absorbed from the GIT
  b. resistant to hepatic metabolism (steroids excluded)
  c. limited in their volumes of distribution (~ ECF)
  d. relatively excluded from the CNS

<table>
<thead>
<tr>
<th>Drug</th>
<th>$V_d$ (ml/kg)</th>
<th>Cl (ml/kg/min)</th>
<th>$t_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>403</td>
<td>1.4</td>
<td>187.3</td>
</tr>
<tr>
<td>Atracurium</td>
<td>130</td>
<td>5.5</td>
<td>19.6</td>
</tr>
<tr>
<td>Gallamine</td>
<td>206</td>
<td>1.2</td>
<td>129.5</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>140-205</td>
<td>1.2-1.6</td>
<td>75-107</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>297-522</td>
<td>1.8-3.0</td>
<td>107-237</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>270</td>
<td>5.2</td>
<td>61.1</td>
</tr>
<tr>
<td>mivacurium</td>
<td></td>
<td></td>
<td>~ 3-5</td>
</tr>
<tr>
<td>rocuronium</td>
<td></td>
<td></td>
<td>~ 60</td>
</tr>
<tr>
<td>pipercuronium</td>
<td></td>
<td></td>
<td>~ 100-120</td>
</tr>
<tr>
<td>doxacurium</td>
<td></td>
<td></td>
<td>~ 100-120</td>
</tr>
</tbody>
</table>

- the protein binding of these agents is variable and the significance debated
- theoretically, decreases in protein binding increasing the free fraction of the drug, increasing the level of neuromuscular blockade
- with the exceptions of suxamethonium and atracurium, 2 or 3 compartment "mamillary" models describe the behaviour of these drugs, ie. clearance occurs only from the central compartment
### Modes of Elimination

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal</th>
<th>Hepatic</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>70-90</td>
<td>10-30</td>
<td>0</td>
</tr>
<tr>
<td>Atracurium</td>
<td>&lt; 10</td>
<td>0</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Gallamine</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>30-80</td>
<td>10</td>
<td>15-40</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>40-60</td>
<td>40-60</td>
<td>0</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>&gt; 25</td>
<td>20</td>
<td>50-60</td>
</tr>
<tr>
<td>Pipercuronium</td>
<td>60-90</td>
<td>10-40</td>
<td>-</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>60-90</td>
<td>10-40</td>
<td>-</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>10-20</td>
<td>80-90</td>
<td>-</td>
</tr>
<tr>
<td>Mivacurium</td>
<td></td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>

### Renal Elimination

<table>
<thead>
<tr>
<th>&gt; 90 %</th>
<th>60 - 90 %</th>
<th>40 - 60 %</th>
<th>&lt; 25 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>gallamine decamethonium</td>
<td><strong>pancuronium</strong> metocurine pipercuronium doxacurium fazadinium alcuronium</td>
<td>tubocurarine</td>
<td><strong>atracurium vecuronium</strong> mivacurium rocuronium (ORG-9426) suxamethonium</td>
</tr>
</tbody>
</table>
Suxamethonium

- suxamethonium is rapidly broken down in the body by butyrylcholinesterase, or "pseudocholinesterase", to the monocholine form
- this has ~ 0.05 times the potency of the dicholine parent
- this is then further metabolised to acetate & choline
- data are difficult to determine, but the elimination half life, $t_{\beta} \approx 5$ min
- the rate of hydrolysis is such that only a small fraction of the administered dose reaches the motor endplate
- termination of action is then by dissociation & diffusion, as there is no pseudocholinesterase at the endplate
- pseudocholinesterase therefore controls the duration of suxamethonium blockade by determining the amount which reaches the endplate
- the effect may therefore be prolonged with both congenital and acquired enzyme abnormalities
- although there has been much publication about factors which influence enzyme activity, few are of clinical significance
- with liver disease and a reduction of enzyme activity to ~ 20%, the duration of succinylcholine increased from ~ 3 to ~ 9 minutes
- even with echothiopate eyedrops and a reduction to almost zero activity, the duration increased to only ~ 14 minutes
- a large study by Viby-Mogensen confirmed that blockade from the usual dose of succinylcholine is only modestly increased by low plasma cholinesterase activity
- this statement does not hold for patients homozygous for the dibucaine resistant gene (see later)

Tubocurarine

- highly water soluble, therefore excreted mainly by the kidneys but also in the bile
- halothane and nitrous oxide/narcotic anaesthesia do not significantly alter the pharmacokinetics
- however, the former reduces the serum [dTC] required to produce neuromuscular blockade
- plasma protein binding in adults is about 45%
- increased requirements of dTC have been reported in patients with elevated gamma globulins, eg. hepatic disease & biliary cirrhosis
- protein binding is less in the neonate c.f. the adult
- in terminal renal failure the elimination half-life is prolonged to ~ 330 minutes and only 10-15% is eliminated through the kidneys
- however, there is no change in the serum [dTC] required for neuromuscular blockade
- that is, there is no alteration of the "sensitivity" of the receptors
**Pancuronium / Vecuronium**

- renal elimination is the major excretory pathway for pancuronium
- in patients with **renal failure**, the elimination half-life of pancuronium is prolonged to a greater degree than for dTC
- in patients with biliary obstruction & hepatic cirrhosis, pancuronium displays,
  i. increased volume of distribution
  ii. reduced plasma clearance
  iii. prolonged elimination half-live

  $\rightarrow$ greatly prolonged neuromuscular blockade

**NB:** effects upon vecuronium metabolism are far less than would be predicted, providing the dose is $< 0.15 \text{ mg/kg}$, there is no prolongation of action

- pancuronium is not extensively protein bound, the free fraction $\sim 90\%$
- about 10-40% is metabolised by deacylation to the following derivatives,
  i. 3-hydroxy
  ii. 17-hydroxy
  iii. 3,17-dihydroxy

- the **3-hydroxy** metabolite possesses the most relaxant activity $\sim 50\%$
- vecuronium is metabolised in a similar manner, being structurally related
- the 3-OH metabolite of vecuronium has $\sim 50-70\%$ of the activity

**Atracurium**

- undergoes **Hofmann elimination**, instability being created by the reverse ester linkages,
  i. physicochemical process independent of enzyme systems
  ii. occurs in the entire volume of distribution
  iii. is temperature and pH dependent

- also subject to enzymatic degradation by **ester hydrolysis** but recent studies conclude that together these may only account for 40-50% of the total metabolism (Fisher *et al.*)
- the immediate metabolites are,
  i. laudanosine - a tertiary amine
  ii. the monoquaternary acrylic acid
  iii. ethyl alcohol

- these are inactive at the neuromuscular junction but are capable of immunogenic responses
- however, atracurium is the least dependent upon renal and hepatic function, being unaffected by the former and either normal or shortened in the later
- **laudanosine** is a direct CNS stimulant, and unlike the parent compound is almost entire reliant on hepatic elimination
- routine blood levels during anaesthesia are well below those required to produce frank seizures
• however, they do result in,
  a. an increase in volatile MAC ~ 30%
  b. an increase in thiopentone awakening level of ~ 20%

• also, laudanosine enhances stimulation-evoked release of *noradrenaline*
• this may, in part, account for the CNS effect

**Doxacurium**

• a new *benzylisoquinoline* ester, is a very potent, long lasting relaxant
• the duration of blockade, in humans, is in the same order as dTC and pancuronium
• the striking dissimilarity between this agent and the later is the wide margin between neuromuscular blockade and either, *vagolytic effects*, *histamine release*, or *sympathetic blockade*
• it is ~ 2x as potent as pancuronium and shows *no* histamine release or cardiovascular effects over the clinical dose range
• it is excreted principally through the *kidney* & bile as the parent drug, ie. *not metabolised*
• preliminary studies indicate an elimination half life, $t_{1/2} \sim 70-100$ min

**Pipercuronium**

• long-acting *steroid* based relaxant, similar potency & duration to pancuronium
• like doxacurium, it is not metabolised and excreted principally through the *kidney* & bile
• duration of action is similarly prolonged in renal and hepatic insufficiency, and in the elderly
• elimination half life, $t_{1/2} \sim 100$ min

**Rocuronium ORG 9426**

• new *steroidal* relaxant of intermediate duration
• kinetic and dynamic parameters are similar to those of vecuronium, except that the *onset* of blockade is faster, being ~ *1.0-1.5 minutes*
• the speed of onset is *unaffected* by priming

  **NB:** based upon the hypothesis of Bowman & Kopman, that onset may be increased by using a molecule of *lower potency*

• that is, the onset of block within the first 2-3 minutes is simply related to the *number* of molecules delivered to the motor end-plate per unit time
• conversely, a short duration is achieved by rapid diffusion from the NMJ receptor and preferably inactivation
• however, rocuronium it is *not metabolised* but eliminated unchanged in the urine & bile
• duration is not prolonged in renal failure, but may be in *cirrhosis*
• the *safety ratio* for *vagolytic* side-effects is ~ 10x less than vecuronium (5 vs. 50)
• there is a modest increase in HR at doses > 0.6 mg/kg

  **NB:** this is seen with all *steroidal relaxants* to varying degrees
Mivacurium

- a new benzylisoquinoline ester, which is hydrolysed by plasma cholinesterase
- the rate of hydrolysis is slightly slower than succinylcholine ~ 70-80%
- the duration of action is ~ 1/2 - 1/3 that of atracurium or vecuronium at high doses
- doses of 3 x ED$_{95}$, or 0.25 mg/kg, the time to 95% twitch recovery was < 30 minutes
- cardiovascular effects are minimal in the dose range 2.0-2.5 x ED$_{95}$, or 0.15-0.20 mg/kg
- rapid bolus injection of larger doses results in histamine release with,
  i. transient facial erythema
  ii. a brief fall in mean arterial pressure

- it does not result in vagal blockade, thus does not result in a tachycardia
- its rate of onset may be increased by "priming"
- good conditions for intubation can be achieved within 1-2 minutes of injection
- reversal becomes debatable due to,
  1. should the already rapid rate of hydrolysis of mivacurium be augmented by administration of anticholinesterase
  2. the differential effects of neostigmine & edrophonium on BuChE and AChE → inhibition of BuChE may actually prolong blockade, due to inhibition of hydrolysis
  3. clinical application of human plasma cholinesterase as the preferred drug to counteract blockade with mivacurium or SCh

**NB:** ALL of the benzylisoquinoline esters share the property of histamine release, for the currently available members of this group, the order of magnitude is,

i. tubocurarine → prominent
ii. atracurium
iii. mivacurium
iv. doxacurium → virtually absent

- the advantage of this group is the relative ease with which their mode of elimination may be modified, thus providing a group of agents with a range of durations
Sugammadex Org 25969

- tradename Bridion, a novel agent for reversal of blockade by rocuronium
- the first **selective relaxant binding agent** (SRBA)
- modified **γ-cyclodextrin**
  - a. lipophilic core and a hydrophilic periphery
  - b. modified by placing 8 carboxyl thio ether groups at the 6-carbon positions
  - c. extends the cavity size allowing greater encapsulation of the rocuronium
  - d. negatively charged extensions electrostatically bind to the positively charged ammonium group as well as contribute to the aqueous nature of the cyclodextrin

- sugammadex's binding encapsulation of rocuronium has been found to be one of the strongest among cyclodextrin and their guest molecules
- rocuronium molecule (a modified steroid) bound within sugammadex's lipophilic core, is rendered unavailable to bind to the acetylcholine receptor at the neuromuscular junction

- the main advantage is reversal of neuromuscular blockade **without** inhibition of **acetylcholinesterase**
- therefore it does not cause the autonomic instability produced by anticholinesterases
- antimuscarinic agents (atropine/glycopyrrolate) do not need to be co-administered
- therefore associated with much greater cardiovascular and autonomic stability
- suxamethonium is often preferred for RSI, when there is uncertainty of endotracheal intubation
- the introduction of sugammadex will make rocuronium usable in these situations
- **recurarisation**, a phenomenon of recurrence of neuromuscular block, may occur where the reversal agents wear off before a neuromuscular blocking drug is completely cleared
- very unusual with all but the longest acting neuromuscular blocking drugs (such as gallamine, pancuronium or tubocurarine)
- occurs rarely with sugammadex, and only when insufficient doses were administered
- sugammadex has some affinity for the aminosteroids vecuronium and pancuronium
- affinity for vecuronium is lower than its affinity for rocuronium, reversal of vecuronium is still effective because fewer vecuronium molecules are present *in vivo* for equivalent blockade
- vecuronium ~ 7x more potent than rocuronium, \( \therefore \) requires fewer molecules for blockade
- sugammadex encapsulates with a 1:1 ratio, \( \therefore \) will adequately reverse vecuronium
- studies looking at suitability in RSI \( \rightarrow \) rapid and dose-dependent reversal of neuromuscular blockade induced by high-dose rocuronium (1.0 or 1.2 mg/kg)
PHARMACODYNAMICS

Depolarising Drugs

- agonists at nicotinic receptors, including nicotine and ACh itself, are capable of blocking neuromuscular transmission
- during normal transmission, the motor endplate is only transiently depolarised by ACh
- ACh rapidly diffuses from the receptor which then repolarises
- if depolarisation persists, an "island" of depolarisation is established in the middle of normally polarised muscle fibre membrane
- this acts as a continuous current sink, drawing ions from the surrounding muscle fibre
- as is characteristic of excitable membranes, with persistent current flow the surrounding Na⁺-channels undergo a conformational change which renders them inactive
- junctional transmission is blocked and paralysis is flaccid
- in chronically denervated fibres, or any condition in which the receptors are delocalised from the motor endplate, this results in widespread depolarisation and direct activation of the contractile mechanism
- this probably occurs in its purest form only in certain muscle groups and under certain conditions
- in many instances it gradually merges into phase II block

- the only depolarising drug in common clinical use is suxamethonium
- effectively two ACh molecules joined through the acetate methyl groups
- this activates prejunctional and endplate receptors, resulting in depolarisation of the membrane, which persists until the drug diffuses away
- the effects are manifest first as muscle twitching and fasciculation, which are followed by the onset of blockade
- the rate of onset differs for different muscle groups in any one species
- in man these are most noticeable over the chest, neck, eyes and abdomen
- at this time the twitch response is reduced, the train of four ratio is close to unity, and neither fade of tetanic response, nor post-tetanic potentiation occurs → "phase I block"

- if repeated doses, or an infusion is given, tachyphylaxis usually becomes evident
- later still, the dosage required to maintain blockade again decreases, with the development of the characteristics of competitive blockade,
  - TOF ratio < 1.0
  - fade of tetanic response
  - post-tetanic potentiation occur → "phase II block"

- little is known about the relationship between concentration and effect for suxamethonium
- the usual onset of action is about 30 secs and the duration of action is normally about 5 mins
Phase II Blockade

- during recovery from this phase of block, anti-AChE agents, which normally intensify phase I block are effective in reversal
- some authors suggest that phase II block is predisposed to by the inhalational anaesthetic agents (G&G), which affect the post-junctional membrane
- possible explanations for the development of phase II blockade include,
  a. depolarising drugs simply behave as partial agonists, a part of their action being receptor antagonism
  b. after prolonged use they may decrease ACh synthesis / mobilisation, therefore act presynaptically
  c. the initial depolarisation may activate a membrane pump, which then repolarises the membrane, despite the continued presence of the depolarising agent

Non-Depolarising Drugs

- these drugs are effectively competitive antagonists at both the pre- & post-junctional receptors
- many of them can, in high concentration, exert a non-competitive, or channel blockade
- these vary considerably in their potencies at other sites, however, at the neuromuscular junction they are qualitatively similar
- increasing serum concentrations are correlated with an increased receptor occupancy and a proportional decrease in the endplate potential
- analysis shows that these agents decrease the frequency of channel opening events, they do not affect the duration of opening or the open channel conductance
- the decrease in endplate potential displays a safety margin for transmission and blockade is not seen until > 70% receptor occupancy
- further, neuromuscular blockade is not complete until ~ 95% receptor occupancy, depending upon the muscle group
- this mechanism results in the steep dose/response curves for these agents
- this has been statistically modelled by the Hill equation and, also, by a normal distribution about the mean concentration required for individual neuromuscular junctional failure

- patch clamp studies indicate that many drugs are capable of entering open channels thereby occluding them, such drugs include,
  a. barbiturates
  b. local anaesthetics
  c. some antibiotics

- other drugs combine with the closed form of the receptor, altering the ACh binding site
- the inhalational agents appear to alter post-junctional membrane function, probably by effects in the lipid matrix
- neuromuscular blocking agents themselves may result in open channel blockade when present in high concentration
- this may be partly responsible for the failure of neostigmine to reverse excessively deep blockade
## Dosage and Duration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Duration (min)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Subsequent</td>
<td>Initial</td>
<td>Subsequent</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>1.0-1.5</td>
<td>3-10</td>
<td></td>
<td></td>
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<tr>
<td>Alcuronium</td>
<td>0.2-0.3</td>
<td>0.05-0.1</td>
<td>45-90</td>
<td>30-45</td>
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<tr>
<td>Atracurium</td>
<td>0.3-0.5</td>
<td>0.1</td>
<td>20-40</td>
<td>15-30</td>
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<td>Gallamine</td>
<td>2.0-3.0</td>
<td>0.4-0.6</td>
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<td>20-40</td>
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<tr>
<td>Pancuronium</td>
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<td>0.02-0.03</td>
<td>45-60</td>
<td>30-45</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.3-0.5</td>
<td>0.07-0.14</td>
<td>45-60</td>
<td>30-45</td>
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<tr>
<td>Vecuronium</td>
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<td>0.01-0.03</td>
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<tr>
<td>mivacurium</td>
<td>0.15-0.25</td>
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<td>10-20</td>
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<tr>
<td>rocuronium¹</td>
<td>0.6-1.0</td>
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<td>30-45</td>
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<tr>
<td>pipercuronium</td>
<td>0.1-0.15</td>
<td></td>
<td>45-90</td>
<td></td>
</tr>
<tr>
<td>doxacurium</td>
<td>0.05-0.08</td>
<td></td>
<td>45-90</td>
<td></td>
</tr>
</tbody>
</table>

¹ less potent agent → larger dose & faster speed of onset

## Commercial Preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Preparation</th>
<th></th>
<th>Dose¹</th>
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</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>SCOLINE</td>
<td>100mg / 2ml</td>
<td>70mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANECTINE</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alcuronium</td>
<td>ALLOFERIN</td>
<td>10mg / 2ml</td>
<td>17.5mg</td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>TRACRIUM</td>
<td>25mg / 2.5ml</td>
<td>28mg</td>
<td></td>
</tr>
<tr>
<td>Gallamine</td>
<td>FLAXEDIL</td>
<td>4% / 2-3ml</td>
<td>175mg</td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>PAVULON</td>
<td>4mg / 2ml</td>
<td>8.75mg</td>
<td></td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>TUBARINE</td>
<td>20mg / 2ml</td>
<td>28mg</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>NORCURON</td>
<td>4mg / 2ml</td>
<td>6.3mg</td>
<td></td>
</tr>
</tbody>
</table>

¹ dose = for 70kg male calculated from mean initial dose above
## Factors Affecting Neuromuscular Blockade

### Drug Interactions

- i. antibiotics
- ii. local anaesthetics and antidysrhythmics
- iii. anticholinesterases
- iv. frusemide & diuretics
- v. calcium channel blockers

### Inhalational Anaesthetic Agents

### Electrolyte Disturbances

- i. hypokalaemia / hyperkalaemia
- ii. hypocalcaemia
- iii. hypermagnesaemia

### Acid-Base Balance

### Temperature

### Disease States

- i. hypovolaemia
- ii. myasthenia gravis & myasthenic syndrome
- iii. the myotonias
- iv. upper & lower motor neurone diseases
- v. renal disease
- vi. hepatic disease
- vii. morbid obesity

### Age
Drugs Interactions

Antibiotics

- the following drugs have been implicated in affecting the level of blockade,
  i. neomycin
  ii. gentamicin
  iii. kanamycin
  iv. clindamycin
  v. streptomycin
  vi. polymyxin A & B
  vii. tetracycline

- the aminoglycosides reduce the quantal release of ACh from presynaptic terminals by competing with Ca++ and their effects are, therefore, reversible with Ca++ salts (MCQ)
- similar effects are seen with tetracyclines, due to chelation of Ca++
- lincomycin and clindamycin effectively block open channels
- other antibiotics effect either the pre- or post-junctional membrane
- antibiotics that are thought to be devoid of neuromuscular action are the,
  1. penicillins
  2. cephalosporins
  3. chloramphenicol

Local Anaesthetics & Antidysrhythmic Agents

- mechanisms of local anaesthetic agents appear to include,
  1. reduce the neuronal release of ACh
  2. stabilisation of the post-junctional membrane
  3. possibly by a reduction in the open channel duration = open channel blockade

NB: this may be similar to the binding of local anaesthetics to the inner aspect of the nerve membrane Na+-channel

- these agents potentiate the actions of both groups of neuromuscular blockers
- phenytoin has been shown to have similar actions
- it was first noted to interfere with neuromuscular transmission by causing exacerbations of myasthenia gravis
- procainamide and quinidine potentiate the action of the neuromuscular blocking drugs, presumably by a stabilising action on the post-junctional membrane
- the calcium channel blockers also potentiate the action of these agents
- possibly by decreasing Ca++-dependent ACh release, but also possibly by direct membrane / channel effects
Anticholinesterase Agents

- neostigmine, pyridostigmine and edrophonium (used as excluded from CNS)
  \[ \text{increased } [\text{ACh}]_{\text{NMJ}} \] & direct effects on the post-junction membrane

- therefore, these agents are used for the reversal of neuromuscular blockade, usually in concert with a muscarinic antagonist
- as ACh is synergistic with the depolarising agents, these intensify the blockade produced by suxamethonium
- they probably also block the action of pseudocholinesterase, therefore affect mivacurium

Frusemide & Diuretics

- frusemide has dose dependent effects,
  1. low doses - inhibits protein kinases
  2. higher doses - inhibits phosphodiesterase

- increases in presynaptic membrane gCa\(^{++}\) are mediated by cAMP dependent channel phosphorylation
- therefore, phosphodiesterase inhibitors will increase ACh release and antagonise competitive blockade
- both the diazides and frusemide appear to have bimodal effects,
  1. low doses potentiating the effects of dTC
  2. higher doses antagonising these effects \( \propto \) ACh release

\text{NB: for frusemide, these effects have been documented as clinically significant}

- the thiazides and ethacrynic acid also potentiate the effects of the neuromuscular blockers
- presumably by a diuresis altered volume of distribution and electrolyte balance
- ?? \text{PDE inhibition} involved in the acute response of CCF to high doses of frusemide

Other Drugs

- \text{lithium} augments the action of both groups of drugs and apparently may unmask myasthenia gravis
- \text{chlorpromazine} potentiates the non-depolarising agents
- \text{D-penicillamine}, used in the treatment of Wilson's disease, causes a myasthenia like syndrome
- \text{azathioprine} antagonises non-depolarising blockade, possibly by inhibiting phosphodiesterase
**Inhalational Anaesthetic Agents**

- all of the inhalational agents stabilise the post-junction membrane, therefore potentiate the effects of the non-depolarising antagonists
- Waud showed that the inhalational agents produce a **dose dependent** reduction in carbacol induced depolarisation of the endplate
- both the **degree & duration** of blockade are increased
- in the presence of 1 MAC of these agents, the doses of the blocking drugs can be reduced by,
  a. ~ 25% with halothane
  b. ~ 33% with enflurane, isoflurane, desflurane
- these reductions are greater than those afforded by nitrous oxide / narcotic anaesthesia
- other mechanisms by which the volatile agents affect neuromuscular blockade include,
  1. a CNS action reducing muscle tone
  2. increased muscle blood flow (isoflurane only)
  3. decrease the endplate sensitivity to depolarisation
  4. action at a site distal to the motor endplate
  5. direct effects on the ACh receptor

**NB:** there is **no** evidence for presynaptic inhibition of ACh release

**Electrolyte Disturbances**

- in accordance with the cord conductance equation, the resting membrane potential is primarily determined by the ratio of intra/extra-cellular **potassium**,  
  a. hyperkalaemia → decreased $E_m$ & partial depolarisation of the membrane  
  → potentiation of the effects of the depolarising agents  
  opposition to the effects of the non-depolarising agents
  b. **hypokalaemia** → increased $E_m$ & hyperpolarisation of the membrane  
  → **potentiation** of the effects of the non-depolarising agents  
  opposition to the effects of the depolarising agents
- studies of diuretic induced hypokalaemia in cats have shown a decreased requirement for pancuronium and that more neostigmine is required for reversal of NMJ blockade
- the release of ACh from the motor nerve terminal is Ca$^{++}$ & Mg$^{++}$ dependent
- increased Ca$^{++}$,
  a. increases the quantal release of ACh
  b. decreases the sensitivity of the post-junctional membrane to ACh
  c. enhances excitation-contraction coupling
• increased Mg$^{++}$,
  a. decreases the quantal release of ACh
  b. decreases the sensitivity of the post-junctional membrane to ACh

  NB: thus, the action of the non-depolarising blockers can be augmented by,
  i. a low serum Ca$^{++}$, or
  ii. a high serum Mg$^{++}$

• in addition, Mg$^{++}$ increases the degree of block produced by the depolarising agents
• this may be relevant during Rx for toxæmia of pregnancy

■ Acid-Base Balance

• respiratory acidosis enhances dTC & pancuronium induced neuromuscular junction blockade and opposes reversal by neostigmine, to which RDM states,

  NB: "it is impossible to antagonise a nondepolarising neuromuscular blockade in the presence of significant respiratory acidoses ($P_{\text{aCO}_2} > 50$ mmHg)

• the effects seen during other disorders tend to be conflicting
• possibly, respiratory alkalosis & metabolic acidosis antagonise neostigmine reversal of neuromuscular junction blockade

■ Temperature

• hypothermia produces profound changes in the pharmacokinetic & pharmacodynamic changes
• hepatic and renal elimination of both dTC and pancuronium, and thus their duration of action are prolonged
• in the case of atracurium, the rate of Hofmann degradation is also reduced
• metabolism of both classes of agents is reduced
• hypothermia also appears to increase the endplate sensitivity to pancuronium, this is not seen with dTC and reason for difference unknown

■ Disease States

• in general, severely ill patients are likely to be more sensitive to neuromuscular junction blocking drugs
• except in states where there is delocalisation of ACh receptors from the motor end-plate

■ Hypovolaemic States

• both the rate of onset and decay of effect, of both groups of drugs can be significantly delayed by decreased muscle circulation
• this can occur with any disease state resulting in a decrease in circulating blood volume
• those agents associated with a significant degree of histamine release may result in, or markedly exacerbate, hypotension

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Myasthenia Gravis & Myasthenic Syndrome

- These patients are often exquisitely sensitive to the non-depolarising agents, while their response to suxamethonium may be reduced
- Neuromuscular blockade is best avoided in these people, and anaesthesia can usually be achieved with volatile agent alone
- Prior to administration of a neuromuscular agent, the level of pre-existing blockade should be assessed by a TOF response
- If the baseline TOF significantly depressed, the addition of further relaxant may result in a block which is essentially irreversible
- If additional relaxation is required, deepening the level of anaesthesia is preferable
- This is a recognised technique, as the disease process often responds to anaesthesia in an unpredictable manner

The myasthenic (Eaton-Lambert) syndrome, is an association between carcinomatous conditions, particularly oat-cell carcinoma of the lung, and motor neuropathy
- Clinically it resembles myasthenia, however, they often show increased sensitivity to both groups and often readily develop phase II block
- Therefore, neuromuscular function should be monitored intraoperatively

The Myotonias

- Patients with myotonia dystrophica, myotonia congenita and paramyotonia congenita, exhibit generalised muscular spasm after the administration of depolarising agents
- Myotonia dystrophica (atrophica) is the most common variety
- In addition to the usual clinical features, cardiac failure and conduction defects are frequently present, as is involvement of the respiratory muscles
- The increased mortality in these patients is partly attributable to respiratory failure in the postoperative period
- The generalised muscle spasms which may follow depolarising agents are not relieved by the administration of a competitive agent
- These patients may respond normally to the non-depolarising agents, as the disease is one of the muscle membrane
- They are also prone to develop apnoea following the administration of sedative or anaesthetic drugs
Upper & Lower Motor Neurone Diseases

- **hemiplegia** from cerebral ischaemia is associated with differing responses to nondepolarising relaxants on the 2 sides of the body
- muscles on the affected side are relatively resistant to blockade
- if this side is adjacent the anaesthetist and more amenable to monitoring, there are 2 possible consequences,
  1. a relative overdose may be administered, making timely reversal difficult
  2. this ensures movement during the procedure is unlikely, as the most resistant muscles are monitored

**NB:** monitoring of blockade should be performed on the unaffected limb

- the use of succinylcholine in such patients is associated with the risk of hyperkalaemia
- the time course of such sensitivity is not well defined, with case reports from,
  a. 1 week to 6 months following the onset of hemiplegia
  b. 3 days following SCI

- patients with mixed LMN disease processes, such as,
  i. amyotrophic lateral sclerosis
  ii. lower motor neurone disease
  iii. syringomyelia

**NB:** may exhibit either an exaggerated or reduced response to the non-depolarising agents, due to delocalisation of the ACh receptors from the motor endplate

- **familial periodic paralysis** may be associated with hypo/normo/hyperkalaemia
- it is characterised by intermittent attacks of flaccid paralysis, usually sparing the bulbar group
- muscle relaxants should generally be avoided if possible
- the potassium status should be managed in a standard fashion

Renal Disease

- agents almost entirely reliant on renal clearance for elimination include,
  i. **pancuronium** > dTC
  ii. pipercuronium
  iii. doxacurium
  iv. gallamine, metocurine, fazadinium, alcuronium and decamethonium

- most other commonly used drugs are partly renally cleared (see above) and have proportional alterations of their elimination half lives
- **atracurium** is the drug of choice for muscle relaxation in renal disease due to its physicochemical elimination
- a number of drugs used in renal disease can significantly affect the action of the muscle relaxants,
  → aminoglycosides, frusemide, azathioprine, methylprednisolone
- **Hepatic Disease**
  - the liver plays only a **minor role** in the elimination of most muscle relaxants, *except*,
    - i. rocuronium
    - ii. tubocurarine
  - therefore, hepatic disease does not influence their use to the same extent as does renal disease
  - **pseudocholinesterase** is synthesised in the liver and its serum levels may fall in advanced cirrhosis
    → prolonged effect of suxamethonium, but not clinically significant
  - alterations in the volumes of distribution do occur, generally increasing, with corresponding reductions in the plasma clearances

- **Age**
  - neonates appear more sensitive to the effects of the non-depolarising agents, and the response of the small infant closely resembles that of the **myasthenic adult**
  - Stead (1955) suggested that neonates are "miniature myasthenics"
  - development of the neuromuscular junction is not complete until ~ 2 months
  - premature infants are more susceptible to post-tetanic exhaustion that are term infants
  - there is dispute among many of the studies as to the increased sensitivity of the neonatal neuromuscular junction
  - in recent years separating the pharmacodynamics from the pharmacokinetics has allowed a more precise answer

  **NB:** neonates and infants display **increased sensitivity** to dTC
  - the dose should be further reduced in the presence of hypothermia, acidosis, or prematurity
  - however, this group has a larger $V_{ass}$, therefore doses are similar to those in the adult
  - the longer elimination half life in neonates calls for administration of subsequent doses at less frequent intervals

  - **vecuronium** & **atracurium** differ from the long acting muscle relaxants
  - infants have an increased sensitivity to **vecuronium** compared with adults
  - however, there is a marked increase in duration of action
  - this relates to a increased volume of distribution, despite a normal clearance
  - thus, vecuronium is a long-action muscle relaxant in the neonate
  - the duration of action of **atracurium** is not significantly different in paediatric versus adult patients,
    - i. volume of distribution increases
    - ii. total clearance increased
    - iii. the half life is unaltered

  - in terms on antagonism, doses of neostigmine and edrophonium used for adults are appropriate for children, although some minor dose variations have been described by Fisher *et al.*
studies are now considering whether elderly patients (> 60 yrs) may respond differently from younger patients to the nondepolarising muscle relaxants

- McLeod et al. found the clearance of pancuronium inversely related to age
- clearance in the 3rd decade being ~ 2x that in the 9th decade
- these investigators agree that the pharmacodynamics of the muscle relaxants are not significantly altered in the elderly
- there is disagreement regarding the elderly and pharmacokinetics
- differing results arise partly due to the presence of concurrent disease in the elderly
- separating the influence of age from that disease being difficult
- Rupp et al. concluded that in healthy 70 to 84 year old patients, the pharmacokinetic / pharmacodynamic response to nondepolarising muscle relaxants does not differ markedly from their younger counterparts
- however, many of the elderly hospital population have disease processes which are associated with altered response to the neuromuscular agents
## ACTIONS AT OTHER SITES & ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Potency</td>
<td>NMJ</td>
<td>Cardiacvagus</td>
<td>SNS ganglia</td>
</tr>
<tr>
<td>Tubocurarine$^3$</td>
<td>1</td>
<td>1.7</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Atracurium</td>
<td>1</td>
<td>0.06</td>
<td>0.03</td>
<td>0.3</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>6</td>
<td>0.05</td>
<td>&gt; 0.004</td>
<td>minimal</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>5</td>
<td>0.3</td>
<td>0</td>
<td>minimal</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>2</td>
<td>0.3</td>
<td>0.25</td>
<td>slight</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.3</td>
<td>1.7</td>
<td>&gt; 0.01</td>
<td>minimal</td>
</tr>
<tr>
<td>mivacurium</td>
<td>minimal</td>
<td></td>
<td></td>
<td>SR = 3</td>
</tr>
<tr>
<td>doxacurium</td>
<td>minimal</td>
<td></td>
<td></td>
<td>SR &gt; 3</td>
</tr>
<tr>
<td>rocuronium</td>
<td>SR$^4$ = 5</td>
<td></td>
<td></td>
<td>minimal</td>
</tr>
<tr>
<td>pipercuronium</td>
<td>SR = 25</td>
<td></td>
<td></td>
<td>minimal</td>
</tr>
</tbody>
</table>

1. Vagal blocking activity is *predominantly* associated with the *steroidal agents*, the "..uronium" group.
2. Histamine release is *predominantly* associated with the *benzylisoquinolone agents*, the "..acurium" group.
3. DTC is used as the reference, its potency at the neuromuscular junction being designated 1.0
4. *Safety Ratio* for NMJ activity versus cardiac vagus, ED$_{50}$'s
Non-depolarising Drugs

- although the main site of action is the *nicotinic receptor* of the neuromuscular junction, the various agents have different propensities to act at other sites, namely,
  
  1. the nicotinic receptor of *autonomic ganglia & adrenal*  
     \[ \rightarrow \text{arterial hypotension} \]
  2. the *muscarinic receptors* in the heart (M₂)  
     \[ \rightarrow \text{arterial hypertension & tachycardia} \]

- pancuronium possesses moderate vagal blockade, but also blocks catecholamine reuptake in postganglionic SNS fibres, thus enhancing the effects of muscarinic block
- histamine release contributes to the CVS effects of dTC, and to a lesser extent alcuronium and atracurium
- *histamine release* has been shown to occur with atracurium, mivacurium and suxamethonium
- the most common effects of histamine release seen after dTC include,
  
  i. erythema of the upper face and neck
  ii. occasionally bronchospasm
  iii. may also contribute to the hypotension seen with dTC

*Histamine Release & Anaphylaxis*

- histamine release is a generic side-effect of the *benzoisoquinoline ester* agents
- the histamine ED₅₀:NMJ-ED₅₀ ratio, reflecting diminished propensity to histamine release, for,
  
  a. dTC \[ \sim 0.7-1.0 \]
  b. atracurium \[ \sim 2-3 \]
  c. mivacurium \[ \sim 3 \]
  d. doxacurium \[ > 3 \]

- the *mast cells* of the skin and internal organs react differently
- the flushing of the skin seen with atracurium is *not* due to generalised histamine release

\[ \text{NB: most drugs administered IV release small amounts of histamine, which are pharmacologically insignificant} \rightarrow \leq 1-2 \text{ ng/ml} \]

- the exception to this is *etomidate*, which appears to have no such effect
- increases of 5-10 fold are required for significant systemic effects
- effects of multiple drugs are additive \( \rightarrow \text{effect} \propto \text{the absolute plasma histamine level,} \)
  
  a. 2-3 ng/ml \[ \rightarrow \text{no clinical significance} \]
  b. < 10 ng/ml \[ \rightarrow \text{urticaria, flushing, tachycardia} \]
  c. > 10 ng/ml \[ \rightarrow \pm \text{life threatening bronchospasm, hypotension & arrest} \]
Neuromuscular Blockers

- STP → drug/plasma protein precipitation ± local urticarial wheal mixed with the following,
  1. alcuronium
  2. atracurium
  3. vecuronium

- these may result in bronchospasm if sufficient microaggregates are swept into the lung

- Watkins et al. (Royal Society 1988), reporting on "life-threatening anaphylactoid reactions",
  a. alcuronium & suxamethonium = most hazardous
  b. pancuronium = safest
  c. atracurium & vecuronium = slightly > pancuronium

  *NB: dTC releases 3-5x the average amount of histamine but carries only a slightly increased risk

- H₁ & H₂ receptor stimulation → mast cell degranulation → eicosanoids, PGF₂α
- the later is an evanescent vasodilator in skin, muscle and splanchnic beds
- the physiological effects can be blocked by,
  1. histamine receptor antagonists * need to block both H₁ & H₂
  2. NSAID's - aspirin, ibuprofen

- Cardiac Vagus Effects

- gallamine was the first agent demonstrated to block M₁-receptors and result in a tachycardia
- binding is actually to an allosteric site, not the ACh site, producing a conformational change in the receptor
- vagolytic activity is seen with all steroidal based agents
- this is measured as the safety ratio for NMJ blockade against vagolytic activity in the cat
- a safety ratio > 5 is required for clinical practice, those for the steroidal relaxants being,
  1. pancuronium ~ 2
  2. rocuronium ~ 5
  3. pipercuronium ~ 25
  4. vecuronium ~ 60
Depolarising Drugs

### Complications of Suxamethonium

<table>
<thead>
<tr>
<th>common</th>
<th>rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasciculations</td>
<td>Severe hyperkalaemia</td>
</tr>
<tr>
<td>Muscle Pains</td>
<td>Prolonged apnoea</td>
</tr>
<tr>
<td>Bradyarhythmias</td>
<td>Malignant hyperpyrexia</td>
</tr>
<tr>
<td>Myoglobinæmia</td>
<td>Masseter spasm</td>
</tr>
<tr>
<td>↑ CPK</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Mild hyperkalaemia</td>
<td>Anaphylactoid reactions</td>
</tr>
<tr>
<td>↑ pressure</td>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>• intraocular</td>
<td>Sinus arrest / asystole</td>
</tr>
<tr>
<td>• intracranial</td>
<td></td>
</tr>
<tr>
<td>• intragastric</td>
<td></td>
</tr>
<tr>
<td>↑ secretion</td>
<td></td>
</tr>
<tr>
<td>• gastric acid</td>
<td></td>
</tr>
<tr>
<td>• bronchial</td>
<td></td>
</tr>
<tr>
<td>• salivation</td>
<td></td>
</tr>
</tbody>
</table>

#### Arrhythmias

- suxamethonium exhibits a number of cholinomimetic actions, acting at,
  - a. parasympathetic & sympathetic autonomic ganglia
  - b. $M_2$ receptors of the heart

- the CVS effects are variable,
  - a. adults who have received premedication with antimuscarinic drugs frequently → tachycardia and increased BP
  - b. children may show bradycardia or sinus arrest, especially if antimuscarinic premedicant has been omitted

- the incidence of sinus bradycardia or a junctional rhythm is greater after a second dose
- under stable anaesthetic conditions, succinylcholine lowers the threshold for catecholamine induce ventricular arrhythmias
Muscle Pains

- common and are due to the widespread fasciculations
- these most commonly affect the neck, shoulder girdle and chest
- their incidence may be reduce with a "priming" dose of non-depolarising agent
- this will also decrease the incidence, or severity of rise in intraocular and intragastric pressure
- increases in plasma creatinine phosphokinase and myoglobin will also be reduced

Hyperkalaemia

- depolarisation normally produces a small rise in the serum [K⁺] ~ 0.5 mmol/l
- where denervation has occurred, or where neural activation is significantly reduced, ACh receptors spread from the neuromuscular junction and suxamethonium induced depolarisation can result in dangerous hyperkalaemia, this may be seen with,
  a. denervation
  b. burns
  c. major trauma
  d. neurologic disease & trauma
  e. severe sepsis
  f. renal failure
  g. cerebrovascular accidents

- this predisposition does not tend to occur immediately but is seen several days after major injury
- it may persist for 2-3 months following burns, or up to 6 months following neurological lesions
- there is a marked increase in receptor density over the entire muscle surface
- the recovery of normal function is delayed by infection or persistent tissue degeneration
- there is one well described case report of hyperkalaemia following a closed head injury
- this should not prevent its use in this setting, however, a hyperkalaemic response is possible
  - the evidence to support renal failure as a predisposing factor has recently been disputed
  - providing the initial serum K⁺ ≤ 5.5 mmol/l there is no increased risk
  - suxamethonium may actually be the agent of choice because of its lack of reliance on renal excretion

Malignant Hyperpyrexia

- suxamethonium can also trigger malignant hyperthermia in genetically susceptible individuals
- ~ 70% of whom will display elevated creatine phosphokinase levels in the resting, fasted state
- in susceptible persons, a negative result should be determined by muscle biopsy studies
- rare in Australia but ? increased incidence in Moaris
- masseter spasm occurs mainly in children
- represents a spectrum of responses, which may be associated with an increased risk of MH
Suxamethonium Apnoea

- prolonged apnoea may result from,
  a. plasma cholinesterase deficiency - acquired
     - congenital
  b. phase II block
  c. drug interactions

- **Acquired Enzyme Deficiency**

  - plasma cholinesterase levels are reduced in the following conditions,
    a. the newborn, reaching adult levels by 2-6 months
    b. patients with acute or chronic liver diseases
    c. malnutrition
    d. pregnancy
    e. collagen diseases
    f. chronic anaemia
    g. uraemia
    h. myxedema
    i. other chronic debilitating diseases
    j. severe burns
    k. chronic pesticide exposure & accidental poisoning
    l. drugs
      i. MAO inhibitors
      ii. trimethaphan
      iii. cytotoxic drugs - azathioprine
      iv. echothiopate eye drops
      v. hexafluorenium bromide, tetrahydroaminocrine
      vi. quinidine
      vii. propanidid
      viii. OCP
      ix. chlorpromazine
      x. pancuronium, neostigmine

  - increased levels are found in obesity, type IV hyperlipoproteinaemia, nephrosis & toxic goitre

  **NB:** a large study by Viby-Mogensen confirmed that blockade from the usual dose of succinylcholine is only *modestly increased* by low plasma cholinesterase activity
Inherited Enzyme Defect

- plasma cholinesterase is coded for by two allelomorphic genes on an autosomal chromosome
- four variants are described,
  1. normal gene N
  2. dibucaine resistant gene D
  3. fluoride resistant gene F
  4. silent gene S

- the most frequent atypical form, the dibucaine resistant gene, has a far lower affinity for succinylcholine at normal serum concentrations
- the population prevalence for the D-gene is ~ 1:53 (reference, doesn't support below)
- the usual laboratory estimates of plasma cholinesterase do not differentiate between the varieties

- Kalow & Genest found that the local anaesthetic dibucaine inhibits normal plasma cholinesterase to a far greater extent than the atypical enzyme
  Def’n: dibucaine number, the percentage inhibition of plasma cholinesterase produced by a standard titre of dibucaine = 10^{-5} mmol/l

- if abnormalities are found, the entire family should be tested
- another cholinesterase variant has been found, the electrophoretic C5-band enzyme, which shows increased plasma cholinesterase activity
- patients possessing the silent gene are extremely sensitive to succinylcholine

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SCh Sensitivity</th>
<th>DN$^1$</th>
<th>FN$^2$</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>normal</td>
<td>~ 80</td>
<td>~ 60</td>
<td>94 (96.2)$^3$</td>
</tr>
<tr>
<td>ND</td>
<td>mildly increased</td>
<td>~ 50</td>
<td>~ 40</td>
<td>4  (3.8)</td>
</tr>
<tr>
<td>DD</td>
<td>greatly increased</td>
<td>~ 20</td>
<td>~ 20</td>
<td>0.036</td>
</tr>
<tr>
<td>NF</td>
<td>mildly increased</td>
<td>~ 80</td>
<td>~ 40</td>
<td>0.5</td>
</tr>
<tr>
<td>NS</td>
<td>normal</td>
<td>~ 80</td>
<td>~ 60</td>
<td>0.5</td>
</tr>
<tr>
<td>DF</td>
<td>greatly increased</td>
<td>~ 50</td>
<td>~ 40</td>
<td>0.02</td>
</tr>
<tr>
<td>DS</td>
<td>greatly increased</td>
<td>~ 20</td>
<td>~ 20</td>
<td>0.02</td>
</tr>
<tr>
<td>FF</td>
<td>greatly increased</td>
<td>~ 60</td>
<td>~ 20</td>
<td>0.0025</td>
</tr>
<tr>
<td>FS</td>
<td>greatly increased</td>
<td>~ 60</td>
<td>~ 20</td>
<td>0.0025</td>
</tr>
<tr>
<td>SS</td>
<td>greatly increased</td>
<td>~ 0</td>
<td>~ 0</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

1 $\text{DN} = \% \text{ inhibition of plasma cholinesterase by dibucaine } 10^{-5} \text{ mmol/l}$
2 $\text{FN} = \% \text{ inhibition of plasma cholinesterase by fluoride } 5 \times 10^{-5} \text{ mmol/l}$
3 frequencies from Wood & Wood
## Contraindications to Suxamethonium

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered Neuromuscular Function</strong></td>
<td>- the myotonias</td>
</tr>
<tr>
<td></td>
<td>- disuse atrophy</td>
</tr>
<tr>
<td></td>
<td>- muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>- motor neurone disease</td>
</tr>
<tr>
<td></td>
<td>- spinal cord injuries</td>
</tr>
<tr>
<td></td>
<td>- Guillain-Barré syndrome</td>
</tr>
<tr>
<td><strong>Risk of Prolonged Neuromuscular Blockade</strong></td>
<td>- atypical plasma cholinesterase</td>
</tr>
<tr>
<td></td>
<td>- altered plasma cholinesterase function</td>
</tr>
<tr>
<td></td>
<td>- prior administration of an anticholinesterase</td>
</tr>
<tr>
<td><strong>Risk of Severe Hyperkalaemia</strong></td>
<td>- severe burns</td>
</tr>
<tr>
<td></td>
<td>- massive trauma</td>
</tr>
<tr>
<td></td>
<td>- sepsis syndrome</td>
</tr>
<tr>
<td></td>
<td>- closed head injuries</td>
</tr>
<tr>
<td></td>
<td>- spinal cord injuries</td>
</tr>
<tr>
<td></td>
<td>- preoperative hyperkalaemia</td>
</tr>
<tr>
<td><strong>Malignant Hyperpyrexia</strong></td>
<td>- unequivocal clinical episode of MH</td>
</tr>
<tr>
<td></td>
<td>- 1st degree relative with unequivocal MH,</td>
</tr>
<tr>
<td></td>
<td>plus raised CPK</td>
</tr>
<tr>
<td></td>
<td>- positive muscle biopsy</td>
</tr>
<tr>
<td><strong>Risk of Malignant Hyperpyrexia</strong></td>
<td>- central core disease</td>
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<tr>
<td></td>
<td>- King-Denborough syndrome</td>
</tr>
<tr>
<td></td>
<td>- possibly related</td>
</tr>
<tr>
<td></td>
<td>Deuchenne muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Schwartz-Jampel syndrome</td>
</tr>
<tr>
<td></td>
<td>Fukuyama muscular dystrophy</td>
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<tr>
<td></td>
<td>Becker muscular dystrophy</td>
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<tr>
<td></td>
<td>familial periodic paralysis</td>
</tr>
<tr>
<td></td>
<td>myotonia congenita</td>
</tr>
<tr>
<td><strong>Open Eye Injury</strong></td>
<td>- unless significant risk to airway</td>
</tr>
<tr>
<td><strong>Raised ICP</strong></td>
<td>- unless significant risk to airway</td>
</tr>
</tbody>
</table>
Reversal of Residual Neuromuscular Blockade

- the antagonism of curare by anticholinesterase drugs was realised by Pal in Vienna in 1900
- he was studying the effects of physostigmine on gut motility in curarized dogs, when he noticed not only was there an increase in gut motility but the animals also started to breath spontaneously

- the density of neuromuscular blockade is directly proportional to the number of molecules present at the neuromuscular junction
- normal transmission can only be re-instituted by anticholinesterase drugs if the concentration has fallen below a critical level
- this applies irrespective of the dose of anticholinesterase given

**NB:** therefore, deep levels of blockade are not amenable to reversal

1. satisfactory clinical antagonism of deep blockade (TOF = 1-2) with long-acting agents requires 20-30 minutes and large doses of neostigmine (0.06 mg/kg)
2. this process is further slowed by the presence of potent inhalational agents
3. the effects of anticholinesterases on BuChE and AChE, and the potential prolongation of blockade with mivacurium
4. the use of anticholinesterases for reversal of mivacurium is questionable
   - in clinical settings reversal is rapid & requires no augmentation
   - large doses of neostigmine are required to prolong the recovery time (5-6 minutes)
5. the potential use of human plasma cholinesterase
   - acceleration of reversal from 100% blockade with mivacurium or SCh
   - rapid restoration of function in the atypical homozygote

■ Anticholinesterases

- neostigmine & edrophonium are the principal agents used for reversal
- mean durations of onset and effect for the reversal of atracurium induced blockade are below

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose mg/kg&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Onset seconds</th>
<th>Outer Limits minutes</th>
<th>seconds</th>
<th>minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
<td>1</td>
<td>225</td>
<td>3.75</td>
<td>92-405</td>
<td>1.5-6.75</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0.08</td>
<td>346</td>
<td>5.8</td>
<td>245-630</td>
<td>4-10.5</td>
</tr>
</tbody>
</table>

<sup>1</sup> these doses are ~ double normal reversal doses
• there is a wide variation between individuals in the depth of block achieved with a standard dose of any one relaxant
• similarly, the length of time before reversal can be attempted also varies widely
• as a general rule, if there is no response to peripheral nerve stimulation, then reversal should not be attempted
• for prompt reversal of blockade,
  a. the ST should be > 20% of the control value
  b. there should be 3 twitches present on a TOF

**NB:** for any degree of spontaneous offset of blockade, that due to an *intermediate* acting agent, such as atracurium or vecuronium, is more rapidly and reliably reversed than the same degree of block due to a longer acting agent, such as dTC or pancuronium,

∴ use infusions of short-acting agents, cf. pancuronium in long cases

• factors which will prolong non-depolarising relaxant activity include,
  1. overdosage
  2. the relaxant administered
  3. the presence of potentiating agents
     i. inhalational agents
     ii. some antibiotics
  4. hypothermia
  5. electrolyte abnormalities
  6. respiratory acidosis & metabolic alkalosis
  7. the age of the patient

• if neostigmine is given to a patient who has virtually recovered from non-depolarising blockade, then clinically significant blockade may result from the anticholinesterase itself
• this appears not to be as great a problem with edrophonium
• thus, if there is good evidence of neuromuscular recovery, TOF > 0.7, no tetanic fade at 50 Hz and clinically good muscle power, then reversal should **not** be given "just-in-case"
• if assessment is uncertain, then edrophonium **0.5 mg/kg** may be administered

• *edrophonium* possesses slightly greater selectivity for nicotinic receptors
• however, in order to prevent bradycardia, bronchospasm, salivation and gastrointestinal hyperactivity an *anticholinergic* should also be administered
• in patients with significant heart disease it is best to match agents with respect to their temporal effects on heart rate
• the best combinations are,
  a. glycopyrrolate ~ 7.0 µg/kg
     neostigmine ~ 0.035-0.08 mg/kg
  b. atropine ~ 10-15 µg/kg
     edrophonium ~ 0.5-1.0 mg/kg
giving atropine & neostigmine will induce an initial tachycardia, followed by a late bradycardia.

- giving glycopyrrolate with edrophonium will result in a bradycardia.
- the "standard" reversal combination,
  i. atropine 1.2 mg ~ 17 µg / kg x 70
  ii. neostigmine 2.5 mg ~ 35 µg / kg x 70

- alternative means of antagonising neuromuscular blockade involve the use of pyridine derivatives
- the first member, 4-aminopyridine, readily crosses the BBB and is unsuitable
- however, 2,4 & 3,4-diaminopyridine are more polar and relatively excluded from the CNS
- these agents act by increasing the presynaptic release of ACh,
  i. increasing the inward Ca++ flux
  ii. decreasing the outward K+ flux
  → prolonging the nerve action potential

- **Monitoring of Induced Twitch**

1. $T_\text{r}/T_1 > 0.7$ is assumed to be evidence of adequate reversal
   - correlation between TOF ratio and degree of blockade for a variety of muscle groups have been well documented
   - clinical practice is to manually estimate the TOF ratio, which has been shown to underestimate the degree of blockade
2. assessment is made at either,
   i. the ulnar nerve of the adductor pollicis muscle, or
   ii. the facial nerve and the frontalis muscle
3. skeletal muscles assessed are not those of interest, ie. the diaphragm & airway groups
4. **diaphragmatic function** returns more quickly than adductor pollicis function
   i. higher muscle blood flow
   ii. different dose-response curve for diaphragmatic fibres
   iii. normal tidal volume requires only ~ 15% of normal muscle function
5. the assumption that diaphragmatic strength will be adequate with normal TOF at the wrist may be inaccurate when work of breathing in increased,
   i. bronchospasm
   ii. partial airway obstruction
   iii. altered lung/chest wall compliance
   iv. use of intercostals is required, which are more susceptible to blockade
6. the **facial muscles** are distinctly more resistant to relaxants than the hand
   i. susceptibility approximates that of the diaphragm
   ii. TOF in the face returns long before TOF at the wrist
   iii. monitoring facial muscles may seriously underestimate airway muscle function
Clinical Assessment of Residual Paralysis

1. **ventilation**
   i. normal $P_{aco2}$, ETCO$_2$ and tidal volume are desirable but **do not** adequately assess the level of residual blockade
   ii. **double-burst stimulation** - better than TOF
   iii. **maximal inspiratory pressure** (MIP) has the following advantages,
       - can be obtained in uncooperative patients
       - quantitative assessment of respiratory muscle strength
       - relatively unaffected by obstructive/restrictive lung disease
       - gives an estimate of respiratory reserve
       → MIP > -25 cmH$_2$O required for *spontaneous ventilation*

2. **airway protection**
   - these muscles are far more sensitive to blockade than the respiratory muscles
   - cases of obstruction/aspiration have been reported following *priming doses*
   - a voluntary sustained head-lift > 5 seconds has been stated to be the most sensitive clinical test of reversal
   - this correlates with a MIP > -55 cmH$_2$O
   - spontaneous ventilation, ability to swallow and protect the airway are usually present at
   → MIP > -45 cmH$_2$O

*NB:* following extubation, the patients ability to protect their airway should be reassessed