Ho Medical ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Neuromuscular Blocking Drugs & Antagonists

Pharm-05A4 Outline the mechanism of action of drugs that inhibit cholinergic transmission at the neuromuscular junction giving examples.

1. Normal cholinergic transmission at the NMJ involves:
    a. Synthesis of ACh: acetyl-CoA + choline → acetylcholine (choline acetyl transferase)
    b. Release of ACh from presynaptic terminal triggered by Ca^{2+} influx (voltage gated channel)
    c. Binding of ACh to Nicotinic receptors causes opening of Nicotinic ion channels → Na enters → post synaptic depolarisation.
    d. Binding of ACh to presynaptic nicotinic receptors further enhances ACh release (positive feedback)

2. Drugs which inhibit transmission
    a. Depolarising NMBD:
        i. Groups –
            1. Aminosteroids: pancuronium, vecuronium, rocuronium
            2. Benzylisoquinoliniums: atracurium, cisatracurium, mivacurium
        ii. Mechanism:
            1. these drugs are large molecules with ionised groups. The ionic portion competitively binds with the α-subunit of the nicotinic receptor without activating the channel (pure antagonist). ↑70% receptor blockade produces decreased response to presynaptic action potential.
            2. Additionally, NDMBs also inhibit presynaptic ACh receptors, which accounts for their titanic fade effect.
        iii. Metabolism: Offset overcome by increasing ACh at junction (AChE inhibitors), or by drug metabolism –
            1. Rocuronium/vecuronium: mainly hepatic metabolism and bile excretion
            2. Pancuronium: hepatic metabolism with renal excretion
            3. Atracurium: 60% plasma cholinesterase, 40% Hoffman
            4. Cisatracurium: 70% Hoffman, 16% unchanged urine
            5. Mivacurium: plasma cholinesterase
    b. Non depolarising:
        i. Suxamethonium
        ii. Mechanism: suxamethonium is an ACh analogue which binds to the 2α units on the nicotinic receptor → activation → opening of channel → Na^+/Ca^{2+} influx → depolarisation (20% receptor occupancy required)
        Unlike ACh, suxamethonium is not metabolised by acetylcholinesterase (AChE) → remains bound to nicotinic receptor → channel stays in open-inactive state → muscle relaxation, no further depolarisation possible.
        iii. Metabolism: Offset via diffusion (down concentration gradient) into plasma, where metabolism occurs via plasma cholinesterases:
        Suxamethonium → succinylmonocholine + choline → succinic acid + 2 choline

    c. Other mechanisms:
        i. ↓ ACh synthesis:
            1. Hemicholinium blocks transport of choline into the nerve terminal

ii. ↓ACh release from presynaptic terminal
    1. Botulinium toxin – directly blocks ACh release, affecting NMJ and parasympathetic transmission.
    2. Aminoglycosides - ↓Ca entry
    3. Ca^{2+} channel blockers - ↓ Ca entry
    4. Tetracycline
    5. ↑Mg^{2+}
    6. Frusemide
iii. ↓End-plate sensitivity at post-synaptic membrane:
    1. LAs
    2. Lithium
    3. ↓K^{+}

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-09B5 Describe the factors that may decrease the clinical response to nondepolarising neuromuscular blocking agents.

1. Non-depolarising neuromuscular blockers are used in anaesthesia to achieve muscle relaxation.
    a. Mechanism: they are competitive inhibitors of the N ACh receptor, which bind reversibly to pre and post-synaptic receptors to prevent their activation by ACh at the motor endplate.

2. Measurement of clinical response: a nerve stimulator is used to test the excitation-contraction response. Typically, a negative electrode is placed over the ulnar nerve, to stimulate the adductor pollicis with a supra-maximal electrical stimulus (60-80mA).
    a. Onset of block – determined by rate at which receptors are occupied → relaxation effect seen occupancy > 75%
        i. TOF: adequate when TOF count = 3 (80% receptors occupied)
    b. Depth block:
        i. Deep – PTC:

PTC	**Clinical**
2-3	No twitch 30min
5	No twitch for 15 min
>15	TOF twitches elicited

        ii. Moderate - TOF
    c. Duration of block – determined by rate at which the drug diffuses out of the NMJ into the plasma.
        i. TOF ratio:

TOF ratio	Clinical
<0.4	Unable to lift head
0.6	Lift head for 3 sec
0.7	↓ VC
>0.8	Normal VC, cough

3. Factors decreasing clinical response:

Factor	**Effect**	**Mechanism**
Measurement		
↓ Muscle BF	↓ speed onset	↑ circulation time → slower delivery to site action
↑ Muscle size	↓ speed onset	Small fine muscles have
Fast twitch	↓ depth, duration	Fast twitch → ↑density Nicotinic ACh R → more resistant to block
Physiochemical		
↑Potency (ED_{95})	Vec > Panc > Miva > Atra > Roc ↓ speed	↑Potency → ↓ dose given → ↓ concentration gradient to NMJ → ↓ speed onset
↓ Dose	↓ depth, duration, speed	↓ Dose → receptor occupation → ↓ speed and depth block
Pharmacodynamic		
Physiological: ↑K, ↑Ca, ↓Mg Alkalosis ↑ temperature Male Sex	 ↓ duration, depth ↓ duration ↓ duration ↓ speed onset, depth	 Ca facilitates ACh release, K depolarises RMP, Mg competes with Ca for ACh release H^+ diffuses out of cell → stable RMP ↑ rate of liver metabolism, and Hoffman degradation Males have ↑ muscle mass

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pathological:		
Drug interactions: AChE inhibitors	Reversal of action	↓ ACh breakdown → ↑ ACh at NMJ → displace drug from receptor → membrane depolarisation
Pharmacokinetic		
Distribution: ↑VD ↓ VD (infusions) ↑ protein	 ↓ speed onset ↓ duration ↓ speed, depth	 Drug diffuses out of central compartment No peripheral redistribution effect of drug Protein binds drug, rendering it inactive
Metabolism: Fast metabolisers / induction	↓ Duration	↑ Metabolism
Elimination: Hydration	↓ duration	↑ rate renal clearance

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-09A3 Outline the factors that determine the rate of recovery from non-depolarising neuromuscular block.

1. Non-depolarising neuromuscular blocking drugs are competitive antagonists at the nicotinic ACh receptors of the NMJ. Hence, recovery depends on the competitive balance of The rate of recovery from NMBDs is measured by the time it takes for returns to 25% T_1 (control twitch height) after an intubating dose of muscle relaxant.

2. Pharmacodynamic factors:
    a. Drug factors:
        i. ↑dose → ↑ recovery time
        ii. Interactions

Prolonged neuromuscular blockade	**Decreased neuromuscular blockade**
Volatile anaesthetics Aminoglycoside antibiotics Local anaesthetics Magnesium Lithium Class I anti-arrhythmics (quinidine) Ca-blockers Frusemide (1mg/kg) Cyclosporin Dantrolene	Anticholinesterase Anticonvulsants (phenytoin, carbamezapine) Frusemide (high doses) Steroids Azathioprine

    b. Patient factors:

Prolonged neuromuscular blockade	**Decreased neuromuscular blockade**
Acidosis (↓metabolism, H/K exchange) ↓ temperature (↓metabolism) ↓Ca (↓ACh release) ↓ K (hyperpolarise RMP) Neonates – incomplete NMJ Elderly - ↓clearance Female - ↓muscle mass NMJ disorders: Myasthenia gravis, burns, SC injury	Alkalosis ↑ temperature ↑ K , Ca ↓ Mg (↓competition with Ca for ACh release)

3. Pharmacokinetic factors:
    a. Distribution: bolus dosing recovery is due to redistribution, whereas infusion recovery is due to metabolism and excretion.
        i. High VD: more rapid recovery from bolus dosing, less rapid recovery from infusion
        ii. Hypoalbuminaemia: ↑ freed rug (minor as most NMBDs are only 10-20% bound)
    b. Metabolism:
        i. Hepatic failure: ↑duration of infusion block
        ii. ↓ pseudocholinesterase: ↑ duration of mivacurium
    c. Excretion:
        i. Renal disease: ↓ clearance → ↑ recovery time

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-04A2/99B10 Outline the factors determining speed of onset of neuromuscular blocking agents.

---

1. Neuromuscular blocking agents cause muscle relaxation by blocking the nicotinic ACh receptor at the NMJ. The speed of onset of muscle relaxation depends on the speed with which at least 20-75% of receptors in a particular muscle group are blocked by the drug. This depends on drug factors, user factors and patient factors. It is measured by TOF stimulation, and defined as the time taken for 95% decrease of T_1 for 2xED_{95} dose of NMBD (intubating dose).
    a. Fast – suxamethonium, rocuronium
    b. Medium – vecuronium, atracurium
    c. Slow – cisatracurium, pancuronium, mivacurium

2. Drug factors:
    a. Pharmacodynamic:
        i. Dose: ↑ dose → faster onset action due to higher concentration gradient for diffusion. This is measured by multiples of ED_{95}.
        ii. Concentration
        iii. Drug-receptor interaction:
            1. Depolarising (suxamethonium) – faster onset of action compared to non-DP agents as they require 20% occupancy for effect, non depolarising require 75% occupancy.
        iv. Drug potency (Bowman principle): inversely proportional to speed of onset.
            1. ↑ potency → ↓ dose → ↓ concentration gradient for diffusion into the NMJ
        v. Drug interactions:
            1. Faster – volatile anaesthetics (↑ muscle BF), opioids, Mg^{2+}, local anaesthetics, aminoglycosides, frusemide
            2. Slower – acetylcholinesterase inhibitors
    b. Pharmacokinetic:
        i. Absorption: site of action affects rate at which drug reaches the NMJ. CVC > PVC > intramuscular.
        ii. Distribution: onset of action depends on distribution of drug to skeletal muscle.
            1. ↑CO → ↑ speed onset, ↓CO (hypovolaemia) → ↓ speed onset
            2. Muscle group type: larynx > diaphragm > adductor pollicis.
                a. Muscles with ↑BF reach equilibrium with plasma faster than lower BF muscles.
                b. Fast twitch have more ACh receptors than slow twitch, and have faster onset.
            3. VD: lower VD → faster effect (greater drug held within plasma for distribution to muscles)

3. User factors:
    a. Speed of injection: faster rate of injection → faster speed onset
    b. Drug interactions: eliminating spare receptors with low dose fast acting NMBDs.
        i. Priming: use of low-dose 10% ED_{95} non-depolarising agent 5 min prior to 2-4ED_{95} of intermediate/long acting NMBD to ↑ speed onset.
        ii. Pre-curarising: use of low dose non-depolarising agents prior to suxamethonium to ↓ extent of depolarisation.

4. Patient factors:

a. Age: elderly ↓ CO → slower onset action
b. Pregnancy: ↑CO, progesterone (displacement) → faster speed action
c. Myasthenia gravis: faster speed onset with NMBDs (fewer NACh receptors), slower onset with suxamethonium

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-06A6 Explain the possible mechanism for prolonged neuromuscular blockade after a four hour procedure using a non-depolarising muscle relaxant.

1. Non-depolarising muscle relaxants work by competitively inhibiting the nicotinic ACh receptor, thus preventing acetylcholine depolarisation of the motor endplate at the NMJ. There are two different groups:
    a. aminosteroids (vecuronium, pancuronium, rocuronium)
    b. benzylisoquinoliniums (atracurium, mivacurium, tubocurarine).

    There are many factors which contribute to prolonged blockade and can be divided into administrative, pharmacodynamic, and pharmacokinetic.

2. Administration: anaesthetist error
    a. Wrong drug: long-acting NMBD
    b. ↑↑ Dose: dose miscalculation, not monitoring degree of blockade

3. Pharmacodynamics:
    a. Physiological interactions:
        i. Hypothermia: ↓ temp (no warming during long case) → ↓ metabolism drug
        ii. Electrolyte disturbance: ↓K, ↑Mg, ↓Ca → ↓Ca release or hypopolarise membrane
        iii. Acidosis: protonated drug forms (bases) have ↑ potency for N ACh receptor
        iv. Pathological states:
            1. Myasthenia gravis – antibodies destroy or block N AChR (less reserve for blockade recovery)
            2. Eaton-Lambert – antibodies destroy or block presynaptic Ca^{2+} channels
    b. Drug interactions:
        i. Volatile anaesthetics – ↓ release ACh from presynaptic terminal, ↓ sensitivity of post-junctional membrane
        ii. Aminoglycosides/tetracyclines – compete with Ca^{2+} at presynaptic terminal
        iii. Li^{2+} - blocks Na channels which conduct AP
        iv. Local anaesthetics – block Na channels which conduct AP
        v. Ca^{2+} block - ↓Ca^{2+} release
        vi. β-blockers
        vii. Diuretics – low dose ↑ duration (high dose ↓ duration)

4. Pharmacokinetics:
    a. Distribution - repeat bolus doses of a lipid soluble drug (vecuronium), can accumulate in peripheral compartments and prolong its action.
    b. Metabolism:
        i. Liver failure
            1. Vecuronium and rocuronium predominantly metabolised and excreted hepatically
            2. Mivacurium requires pseudocholinesterase
    c. Elimination:
        i. Liver failure – as above, elimination of laudanosine
        ii. Renal failure – pancuronium 80% renal elimination

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-02B5/96B16 Outline the possible reasons for prolongation of paralysis induced by an intravenous dose of 1 mg.kg-1 of suxamethonium. Briefly indicate the consequences of such a prolonged block.

---

1. Suxamethonium is a depolarising muscle relaxant used generally for rapid sequence induction.
2. Mechanism of onset / offset:
    a. Dose 1mg/kg
    b. Onset 45 sec
    c. Usual duration 10min
    d. Mechanism: suxamethonium acts as an agonist at the nicotinic ACh receptor, causing depolarisation. However, unlike ACh, it is not metabolised by acetylcholinesterase, and hence blocks the ACh channel in the open inactive state.
    e. Duration – determined by diffusion away from the receptor, into the plasma where it is metabolise by pseudocholinesterase. Thus, alterations in the concentration or activity of this enzyme will affect duration of action.
    Suxamethonium → succinylmonocholine + choline → succinic acid + 2choline

3. Inherited factors: genetic variation among individuals can result in reduced plasma cholinesterase activity. There are 4 different alleles – Eu (normal), Ea (abnormal 4% heterozygote), Es (silent), Ef (fluoride resistant). Homozygotes have a markedly prolonged and heterozygotes a moderately prolonged recovery. The efficiency of the enzyme can be measured with the dubicaine number: the % pseudocholinesterase blocked by $1x10^{-5}$mmol/L dubicaine with benzylcholine. Normal enzyme is 80%, and this decreases in proportion with degree of abnormality.

Genotype	**Duration**	**Dibucaine number**
Eu:Eu	Short 10 min	80
Eu:Ea 4% population	Medium 30 min	60
Eu:Es	Medium	80
Eu:Ef	Medium	75
Ea:Ea	Long 3-8 hours	20
Es:Es	Long	-
Ef:Ef	Long	70

4. Acquired factors: pseudocholinesterase is a glycoprotein synthesised in the liver. Factors which ↓ synthesis include -
    a. Liver disease
    b. Malnutrition
    c. Renal failure
    d. Cardiac failure
    e. Thyrotoxicosis
    f. Pregnancy - ↓40% activity, but this is offset by ↑Vd which balances out loading dose.

5. Pharmacodynamic factors:
    a. Myaesthenic syndrome
    b. Electrolyte imbalance - ↑Mg^{2+}, ↑K^{+} (easier for sux to depolarise membrane)
    c. Hypothermia - ↓enzyme activity
    d. Drug interactions –
        i. Acetylcholinesterase inhibitors prolong phase I block (inhibit AChE and plasma cholinesterase)
        ii. Competition for pseudocholinesterase binding – Mivacurium, ester local anaesthetics, MAOIs

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

iii. Chemotherapy ↓ level – methotrexate

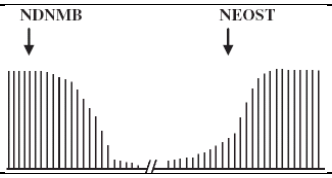
6. Consequences:
    a. Clinical:
        i. Not-intubated: apnoea, hypoxia, conscious distress
        ii. Intubated: ↑ risk barotraumas, myopathy, aspiration
    b. Treatment –
        i. Mechanical ventilation and sedation in an ICU environment
        ii. Reversal - FFP
    c. Investigations –
        i. Dubicaine number
        ii. Family testing
    d. Education –
        i. Avoidance of other drugs – mivacurium, ester local anaesthetics

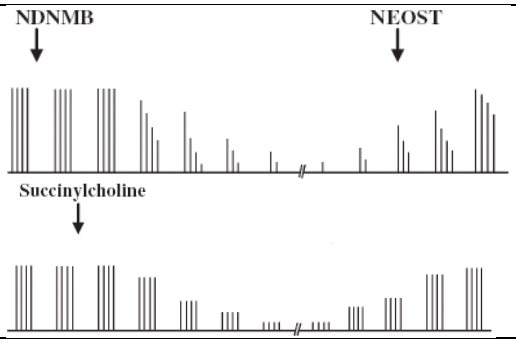
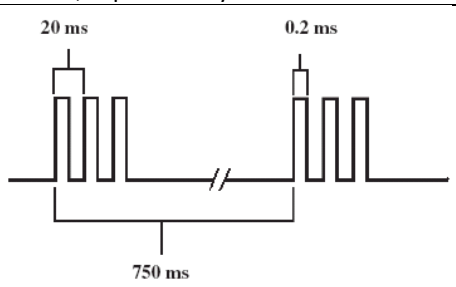
Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-10A2/94 Describe the methods of determining depth of neuromuscular block and list the advantages and limitations of each.

1. Neuromuscular block is determined by using a nerve stimulator is used to test the excitation-contraction response. Typically, a negative electrode is placed over the ulna nerve, to stimulate the adductor pollicis with a supra-maximal electrical stimulus (60-80mA). The common peroneal and facial nerves can also be used.

	Single twitch	**Tetanic stimulation**	**PTC**
Method	Single supramaximal stimulus at 0.1-1Hz for 0.1msec	Supramaximal stimulus 30-200Hz (usually 50Hz) for 5 sec. 50Hz 5 sec → equivalent to maximal voluntary effort.	Supramaximal stimulus applied 50Hz 5sec → 3 sec break → 1Hz stimuli
Diagram			
Use	Crude assessment of blockade at induction.	Assess residual neuromuscular blockade for nonDP NMBD.	Assess deep block, residual blockade when no response to TOF count.
Measurements	Twitch height	Fade	Count number of twitches post tetanus (post-tetanic facilitation)
Result	No reduction < 75% occupancy Decreased > 75% occupancy	Normal: no tetanic fade Phase I: ↓ strength, no fade Phase II: ↓ stretch, fade Absence fade → full muscular power	PTC 2-3 no twitch response 30 min PTC 5 no twitch response 15 min PTC > 15 twitch response on TOF count
Advantage	Quick, easy	Sensitive for residual block, deep paralysis	Sensitive for residual block, deep paralysis
Disadvantage	Require control twitch height before giving NMBD. Poor indicator of depth of paralysis May appear normal when considerable weakness	Unpleasant if patient conscious Muscular pain No additional information to TOF unless combined with PTC	Unpleasant if patient conscious Muscular pain

	TOF	**DBS**
Method	4 supramaximal stimuli 2Hz for 2 sec Must have 10 sec break before re-stimulation	2 x 50Hz tetanic stimuli, 3 bursts lasting 20msec, separated by 750msec.
Diagram		

Use	Assess recovery from moderate-deep blockade esp. NDNMB (residual curarisation). Less useful for monitoring depth or suxamethonium.	Assess residual blockade Detect small degrees of block (superficial block)
Measurements	TOF ratio = 4^{th}:1^{st} TOF count	1^{st} burst sum: $T_1 + T_2 + T_3$ 2^{nd} burst sum: $T_4 + T_5 + T_6$ DBS ratio = $1^{st}/2^{nd}$ DBS Non-DPMR → reduction of 2^{nd} burst (fade)
Result	TOF count 4 < 75% blockade 3 - 75% depression of T_1 2 – 80% depression of T_1 1 – 90% depression of T_1 No twitches – 100% blockade TOF ratio > 0.7 → adequate respiration, 75% blockade TOF ratio <0.9 mild residual block TOF < 1 → >70% blockade	Normal: 2 short muscle contraction of equal force Partial blockade: 2 twitches which are different and display post-tetanic facilitation and fade.
Advantage	Visual assessment Not as painful	More accurate than TOF visually for residual blockade
Disadvantage	Not useful for assessment of residual neuromuscular blockade or adequacy of reversal. Difficult to elicit TOF ratio.	

2. Clinical measurement: without nerve stimulation

Measurement	**Receptor block**	**TOF**
Cough, Normal VC	< 25%	>0.8
Hold head up 5 sec	< 30%	0.6
TV 10mls/kg, cough, sustained hand grip	50-80%	

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-08A7 Describe the terms train-of-four stimulation and double burst stimulation with respect to the peripheral nerve stimulator. Describe their advantages and disadvantages when used to evaluate non-depolarising neuromuscular blockade.

1. Neuromuscular blocking drugs are monitored by examining the effect they have on muscle contraction following a controlled stimulation of a motor nerve.

2. Method:
    a. Skin cleaned
    b. Nerve stimulators are placed over nerve (negative electrode):
        i. Ulnar – adductor pollicis (pharyngeal mm recovery)
        ii. Tibial – flexor hallucis brevis
        iii. Facial – orbicularis oculi (intubating conditions)
    c. Supramaximal stimulus delivered to ensure depolarisation of all composite nerve fibres (usually 60-80mA for 0.1ms)

	Train of Four	**Double Burst**
Definition	4 x 0.1msec stimuli at 2Hz (0.5 sec apart) frequency and 60-80mA.	2 x bursts of 50Hz titanic stimulation (3 x 0.2msec stimuli) at 750msec interval, and 60-80mA.
Measurement	TOF ratio: measuring height 4^{th} twitch:1^{st} twitch TOF number: measure number of successful twitches in response to TOF	DBS ratio: measure response 2^{nd}: 1^{st} stimulation
Outcome	TOF ratio T_4:T_1 < 1 = 70% occupancy T_4:T_1 = 0.75 = 75% occupancy TOF number 3 = 80% occupancy 2 = 85% occupancy 1 = 90% occupancy T_4:T_1 > 0.8 → cough, N VC, return pharyngeal function T_4:T_1 = 0.7 → ↓VC, diaphragm recovery T_4:T_1 = 0.6 → lift head 3 sec T_4:T_1 < 0.4 → unable to lift head	Normal: DBS ratio equal Partial paralysis: DBS ratio < 1 (titanic fade) Fade of 2^{nd} impulse occurs when TOF < 0.6
NDMR vs. DPMR	DPMR: Twitch height reduced, TOF 1 NDMP: graded ↓TOF ratio	
Advantages	More sensitive than single twitch Used in absence of absolute control value Less painful than tetanus Can be repeated more frequently Does not affect degree of NM block	Reliable recovery Shorter duration than tetanus so less painful ↑ sensitivity compared to TOF for evaluation of fade
Disadvantages	TOF ratio difficult to assess in practice Not accurate without acceleromyography Not useful for residual NM blockade or adequacy of reversal	

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Additional Notes:

3. Depolarising NM blockade

- The intensity of response to stimulation is changed, while the character is not.

4. Non-depolarising NM blockade

- The NPMRs exhibit:
  - Post-tetanic facilitation
  - Poorly sustained tetanus response due to blockade of pre-synaptic ACh receptors

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-99A12/90 Explain the phenomena known as fade and post tetanic facilitation associated with the use of neuromuscular blocking agents.

1. Definitions: phenomena which occur in the presence of non-depolarising neuromuscular blockade, or phase II blockade (depolarising).
    a. Fade –repeated frequent stimuli of same intensity results in gradual reduction of twitch height.
    b. Post-tetanic facilitation – following titanic stimulation, a delay (classically 3 sec → 6min) produces potentiation of twitch height with a subsequently applied supramaximal stimulus (60-80mA).

2. Measurement: Neuromuscular blocking drugs are monitored by examining the effect they have on muscle contraction following a controlled stimulation of a motor nerve. Nerve stimulators are placed over a nerve (negative electrode), and deliver a supramaximal stimulus to ensure depolarisation of all composite nerve fibres (usually 60-80mA for 0.1ms). Tetanic stimulation has previously been used to evaluate residual NM blockade. This is no longer done due to pain and use of TOF stimulation.

3. Normal NMJ activation
    a. Release of ACh from presynaptic terminal triggered by Ca^{2+} influx (voltage gated channel)
    b. Binding of ACh to Nicotinic receptors causes opening of Nicotinic ion channels → Na enters → mEPP generation → summation of multiple channel opening → threshold → depolarisation → action potential in myocytes → Ca^{2+} influx → myocytes contraction (twitch)
    c. Binding of ACh to presynaptic nicotinic receptors further enhances ACh production and release (positive feedback)

4. Non depolarisation NMBDs competitively inhibit the nicotinic ACh receptors at both the post-synaptic and pre-synaptic membranes.
    a. Fade – the blockade of pre-synaptic ACh receptors by NDMRs inhibits positive feedback production and release of ACh on repeated stimulation. This is best demonstrated by a train of four stimulus, where 4 supramaximal stimuli are delivered 0.5 sec apart.
    b. Post-tetanic Facilitation – a titanic stimulus results in ↑Ca^{2+} mobilisation and/or ↑ACH mobilisation at the pre-synaptic terminal. After a delay, subsequent electrical stimuli cause ↑↑Ca^{2+} release → ↑↑ACh release → ↑ muscle twitch height.
    c. Post-tetanic count – used to assess degree of neuromuscular blockade. Following a titanic stimulus, supramaximal stimuli are given at 1Hz, starting 3 sec after. The count is the number of twitches (which decrease in size) achieved → inversely proportional to degree of block. Useful in deep block (>95% occupancy) when TOF or single twitch does not evoke stimulus. PTC = 0 deep block, 5-7 (return of TOF).

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-01A14/97B11 Give examples of drugs that enhance the action of the non-depolarising neuromuscular blocking agents at the neuromuscular junction. Briefly describe the mechanisms of these interactions.

1. Non-depolarising neuromuscular drugs are muscle relaxants which work by competitively blocking the nicotinic ACh receptor at the NMJ, thus preventing acetylcholine depolarisation of the motor endplate at the NMJ. Drugs enhancing the action at the NMJ, thus act at either the presynaptic terminal, synaptic cleft, or post-synaptic membrane.

Drug	**Presynaptic Ach release**	**Post-synaptic membrane**
Volatile anaesthetics	↓ACh release (enflurane > sevoflurane > halothane > N_2O)	↓ sensitivity of membrane ↓ muscle tone
Local anaesthetics	↓ACh release	↓Na^+ conductance ↓ sensitivity of membrane
Aminoglycosides	↓ACh release by competing with Ca^{2+}	↓ sensitivity of membrane
Lithium	No	↓ sensitivity of membrane
Ca^{2+} channel blocker	↓ACh release	↓Ca availability for excitation contraction coupling
Diuretics	↓cAMP release → ↓ACh	No
Mg^{2+}	↓ACh release by competing with Ca^{2+}	↓ sensitivity of membrane
Quinidine	↓Ach release	No
Suxamethonium	No	Block spare receptors – phase II block
Non-DP MR	↓ACh release (bind to presynaptic ACh receptor) → prevent positive feedback ACh release	Block spare receptors – phase II block

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-07B6 Describe how suxamethonium produces neuromuscular blockade. What is the mechanism of recovery of neuromuscular function and what mechanisms may be involved in Phase II block?

---

1. Suxamethonium is a depolarising muscle relaxant used most commonly for rapid sequence induction. It is given in doses of 1mg/kg boluses.

2. Mechanism of action:
    a. suxamethonium acts as an agonist at the nicotinic acetylcholine receptor at the neuromuscular junction.
    b. Like acetylcholine, its binding to the α-subunits opens the ligand gated channel, allowing influx of cations (Na/Ca) → membrane depolarisation of the skeletal myocytes → contraction → fasciculations of face, hands then limbs.
    c. Unlike acetylcholine, it is not metabolised by acetylcholinesterase (AChE), and hence, remains in the NAChR for longer, blocking it in the open-inactive state → inability to repolarise → subsequent relaxation
    d. Unlike non depolarising NMBDs, it has no activity at pre-synaptic N ACh receptors.
    e. Relaxation requires > 20% receptor occupancy. This is called phase I block characterised by:
        i. ↓ amplitude twitch to stimulation
        ii. Sustained response to continuous stimulation → no fade
        iii. TOF ratio > 0.7
        iv. No post-tetanic potentiation
        v. Augmentation of block with acetylcholinesterase

3. Mechanism of recovery:
    a. Recovery depends on diffusion of suxamethonium out of the receptor site, into the plasma down its concentration, so that ACh can bind to cause contraction.
    b. Suxamethonium is rapidly metabolised in the plasma by pseudocholinesterase enzymes → succinylmonocholine+ choline → succinic acid + 2choline. This metabolism maintains a concentration gradient which promotes diffusion of the drug out of the receptor site.

4. Phase II block: not 100% understood
    a. This is relaxation of the skeletal muscle that occurs with ↑ doses of suxamethonium (>2mg/kg), or with non-DP muscle relaxants. It is characterised by:
        i. ↓ amplitude to twitch stimulation
        ii. Fade on continuous stimulation
        iii. Post-tetanic facilitation
        iv. TOF ratio < 0.7
        v. Reversibility with anticholinesterases, potentiation of non-DP neuromuscular block
    b. Proposed mechanism:
        i. Prolonged binding of suxamethonium to NACh receptor results in desensitisation of receptors to ACh following drug offset and repolarisation.

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-06B4 Describe the advantages and disadvantages of rocuronium for rapid sequence induction.

1. Rapid sequence induction is a technique designed to secure the airway quickly in patients at risk of aspiration, classically using IV induction agents, and a muscle relaxant for rapid paralysis and intubation. Important elements of RSI include:
    a. Rapid onset (often used in emergency situations)
    b. Rapid offset (procedure is brief)
    c. Consideration of use with IV induction agents
    d. Consideration of patient indications –
        i. Non fasting
        ii. Pregnancy
        iii. Difficult intubation
2. While suxamethonium is usually used as the muscle relaxant, rocuronium is considered a 2nd line agent for several reasons.

Property	**Rocuronium**	**RSI suitability**
Physiochemical		
Group	Non-DP muscle relaxant	Adv: unlike sux, no fasciculations → less post-op myalgia
Formulation	Stable in environment No special storage conditions	Adv: sux needs refrigeration, other non-DPMR need reconstitution (vec, miv)
Interactions	Incompatible with thiopentone, methohexitone, diazepam	Dis: cannot be mixed in same injection with thiopentone, methohexitone, diazepam
Pharmacodynamic		
ED_{95} (mg/kg)	0.3	Dis: more potent than sux (ED_{95} = 0.5), slower onset action
Dose	0.6mg/kg	
Speed onset	1-2min normal dose 30sec 4x ED_{95}	Dis: Not quick enough for RSI Adv: quicker onset than other non-DPMR, but ↑ dose → longer duration
Duration	20-35min 2x ED_{95} 1 hour 4x ED_{95}	Dis: sux much quicker offset (5-10 min) Adv: ↓ duration compared to other non-DP MR
CVS	Stable	Adv: sux causes initial ↑HR, then subsequent ↓HR due to muscurinic agonist effect
CNS	Nil effect ICP/IOP	Adv: sux can cause ↑ICP/IOP
GI	Nil effect	Adv: sux can cause ↑ gastric pressure → theoretical aspiration risk
Histamine	rare	Adv: sux has higher incidence of allergy Dis: cross reactivity with pan, vec
MH	Low or no trigger MH	Adv: sux and others associated with MH
Special groups	Nil contraindications in paraplegia, burns, SC injury, LMN disease Safe in paeds	Adv: sux can cause ↑K in all these groups, sux less recommended in paeds due to undeclared muscular dystrophy → ↑K
Pharmacokinetic		
Distribution	VD = 0.2L/kg Protein binding = 10%	
Metabolism	< 5% metabolised CL = 4mL/kg/min	Adv: greater predictability as minimal metabolism before D-R interaction, unlike sux where 80% metabolised prior to NMJ action, unaffected by pseudocholinesterase (good alternative to genetic variants)
Elimination	60% bile ,40% urine $T_{1/2}$ = 100min	Dis: elimination drug impaired in hepatic and renal disease → ↑ duration action

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-03A8 Describe the onset and offset of neuromuscular block at the diaphragm, larynx and adductor pollicis after administration of 2.5 x ED95 dose of vecuronium. Comment on the differences observed. What are the clinical implications of these differences?

---

1. Vecuronium is a aminosteroid non-depolarising muscle relaxant. Like all NMBDs, its potency is measured by ED_{95} which is the dose of drug required to produce 95% suppression of a single twitch response measured in the adductor pollicis. In general 2.5xED_{95} is dose required for optimal intubating conditions.
    a. ED_{95} = 0.05mg/kg
    b. Intubating dose = 0.1-0.15mg/kg

2. Onset:
    a. Mechanism – onset of muscle relaxation (↓ twitch height) requires blockade of nicotinic receptors at the NMJ at generally > 75% occupancy by vecuronium. The speed of onset is determined by the speed at which the drug diffuses down concentration plasma → NMJ:
    b. Factors:
        i. Muscle blood flow – allows more rapid diffusion and equilibration between plasma and NMJ → larynx /diaphragm > AP
        ii. Muscle size – small fine muscles blocked before larger ones → larynx > diaphragm
        iii. Muscle type – slow twitch have less density of NAChR → more quickly reach required receptor occupancy → faster onset. Larynx/diaphragm have ↑ fast twitch → ↑ resistance.
        iv. Onset: eyes>*larynx >trunk> diaphragm > AP*

3. Offset:
    a. Mechanism – offset of muscle relaxation requires ACh binding at NACh receptor causing depolarisation at the motor end-plate. This requires diffusion of vecuronium away from the NMJ → plasma.
    b. Muscle characteristics:
        i. Blood flow: allows maintenance of concentration gradient so drug can diffuse from NMJ → plasma.
        ii. Muscle type – as above, fast twitch muscles recover more quickly, as they have more “spare receptors”.
        iii. Offset: *diaphragm > larynx > AP*

4. Clinical implications:
    a. Time to recover is not easily measured by normal accessible methods
    b. General:
        i. Onset: Larynx and diaphragm may have started to recover at time of maximal onset of AP (faster onset action)
        ii. Offset: by the time AP has recovered, diaphragm and larynx have recovered (faster offset). This can be safely assumed from external TOF stimulation.
        iii. Orbicularis oculi activity may more closely affect larynx activity.

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-98B13 Draw and explain the characteristics of a log dose-response curve that describes the major clinical effect of vecuronium. List factors encountered in clinical practice that may alter this curve.

---

1. Vecuronium is an aminosteroid non-depolarising neuromuscular muscle relaxant.

2. Log dose-response curve: log dose vs. log effect (% ↓ in adductor pollicis twitch height)
    a. Landmark: ED_{95} = 0.05mg/kg
    b. Take-off delay:
        i. minimal effect seen at low doses.
        ii. Due to abundance of 'spare' nicotinic receptors at the NMJ
    c. Steep slope:
        i. Rapid increase between 75-100% occupancy
        ii. Due to occupancy of non-spare receptors
    d. Plateau:
        i. Flat upper portion whereby ↑ dose → nil further observable change in twitch
        ii. Due to all NMJ receptors already being blocked

3. Comparison with other non-DP blocking agents:

Drug	**ED_{95}**	**Efficacy**
Vecuronium	0.05	Same
Rocuronium	0.3	
Pancuronium	0.06	
atracurium	0.2	

4. Factors shifting curve:

Factor	**↓ Potency (R shift)**	**↑ Potency (L shift)**
Patient factors	↓ Age	↑ Age Disease – myasthenia gravis, burns
Pharmacodynamic	Acetylcholinesterase inhibitors	Drugs: volatile anaesthetics, LAs, aminoglycosides, Ca^{2+} blockers, diuretics, lithium Physiological: acidosis, ↑Mg^{2+}, ↓K^{+},
Pharmacokinetic		Hypothermia (↓ metabolism)

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-00B16/93/92 Compare and contrast the pharmacology of atracurium and cis-atracurium.

1. Atracurium and cisatracurium are non-depolarising neuromuscular blockings drugs. Atracurium is a racemic mixture of 10 different isomers around 4 chiral centres, whereas cis-atracurium is a pure enantiomer of atracurium.

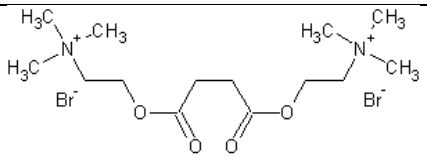
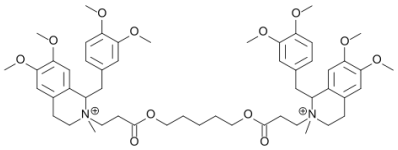
Property	**Atracurium**	**Cis-atracurium**
Physiochemical		
Group	Benzylisoquinolinium	Benzylisoquinolinium
Isomer	Racemic, 4 chiral centres, 10 stereoisomers. 15% by weight cis-atracurium, accounts fro 50% relaxant activity	Pure stereoisomer – R-cis, R^1-cis-isomer
Presentation	10mg/mL (1%), pH 4, store 4°	2mg/mL (1%), pH 4, store 4°
ED_{95} / dose	0.2 / 0.5mg/kg	0.05 / 0.2mg/kg (4xpotency)
Onset	1.5-2min	3-5min (longer)
Duration	30-40min	20-30min
Pharmacodynamics		
Mechanism	Competitive antagonist at the N Ach receptor. Binds to α-subunit and prevents binding of ACh to nicotinic receptor, preventing cation-channel opening of receptor.	
Use	RSI	RSI
CVS	Histamine effect ↓SVR, BP	Stable
Resp	Histamine effect bronchospasm	Stable
CNS	Nil change ICP/IOP	Nil change ICP/IOP
GI	Nil effect LOS pressure	Nil effect LOS pressure
Side-effects	Histamine release Critical illness myopathy	Nil histamine release
Special population	Safe children, elderly	Safe children, elderly
Drug interactions	Potentiation – volatile anaesthetics, LAs, Ca blockers, diuretics, Inhibition – acetylcholinesterase inhibitors	
Physiological	Acidosis – accelerates ester hydrolysis Electrolytes - ↓K, Ca, ↑Mg potentiates effect Dehydration, acidosis → ↑ duration action	
Pharmacokinetics		
Distribution	VD = 0.15L/kg Protein binding 15%	VD = 0.15L/kg Protein binding 15%
Metabolism	Non-specific esterase 60% Hoffman degradation 40% → laudanosine + quaternary monoacrylate (non-active)	Hoffman degradation 77% → laudanosine + quaternary monoacrylate (non-active)
Elimination	Urine elimination metabolites	Urine elimination metabolites 16% unchanged
Organ failure	Generally no effect	Generally no effect

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-98A15 Compare the metabolism of suxamethonium to that of atracurium. 83%

1. Suxamethonium is a depolarising neuromuscular blocker used for muscle relaxation for rapid sequence induction. Atracurium is a non-depolarising benzylisoquinolinium neuromuscular blocker, short acting and also used for rapid sequence induction.

Property	**Suxamethonium**	**Atracurium**
Group	DP muscle relaxant	Non-DP muscle relaxant Benzylisoquinolinium
Structure		
Enzyme	Plasma cholinesterase	Non-specific esterase 60% Hoffman reaction 40%
Synthesis	Liver	Non-liver dependent
Reaction	Diffusion of suxamethonium away from NMJ → plasma. Suxamethonium → succinomonocholine + choline → succinic acid + choline	Esterase: atracurium → laudanosine + quaternary alcohol + acid Hoffman: atracurium → laudanosine + quaternary monoacrylate
Metabolites	Succinylmonocholine: weakly active at NMJ	Laudanosine: no NMJ activity, but causes seizures in animal studies (glycine antagonist). Cleared by liver and kidneys
Location	Plasma	Plasma Peripheral compartments
Duration action	5-10min	20-30min
$T_{1/2}$	0.5-1min (difficult measure)	13-20min
Genetic factors	Eu:Ea/Es/Ef – 30 min duration Ea:Ea – 3-8 hour duration	
Physiological factors	Liver, renal, cardiac, thyroid disease → ↓ Electrolyte - ↑K, ↑Mg, ↓Ca Acidosis Hypothermia slows metabolism	Acidosis accelerates esterase Acidosis and hypothermia slow Hoffman reaction Safe in liver and renal failure Electrolyte - ↓K, ↑Mg, ↓Ca
Drug factors	Competition – mivacurium, ester LAs.	Competition - remifentanyl Facilitation action (not metabolism) – volatile, ester LAs, Ca blockers, aminoglycosides, lithium, diuretics

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

1993/90 What is the dibucaine number? What factors may alter plasma cholinesterase activity and how can this activity be measured.

1. Plasma cholinesterase is an enzyme synthesised in the liver, released in the plasma, responsible for the enzymatic metabolism (by hydrolysis) of important anaesthetic drugs – suxamethonium, mivacurium, ester local anaesthetics, and trimethepan.

2. Activity: the hydrolysis of these drugs into inactive forms is important in determination of duration of action
    a. Suxamethonium → succinylmonocholine → succinic acid + choline

3. Factors affecting activity:
    a. Inherited:
        i. 4 alleles: Eu = normal, Ea = abnormal (4%), Es = silent (1%), Ef = fluoride deficient (0.5%)
        ii. Pseudocholinesterase deficiency – AD, 1:500 homozygote (dubicaine number 20); heterozygote 1:3000 (dubicaine 40-60) results in ↑↑ duration action suxamethonium, mivacurium, and ester LAs.
    b. Acquired:
        i. Liver disease - ↓ production
        ii. Cardiac, renal disease, thyrotoxicosis
        iii. Pregnancy - ↓ production
    c. Drug interaction:
        i. Anticholinesterase (edrophonium, neostigmine) → ↓ activity. Recovery slow, at 30min after → 50% activity
        ii. LAs (dibucaine) – similar properties to plasma CE, so it ↓ activity by 80%
        iii. Metaclopramide, ketamine, lithium, OCP, trimethepan

4. Dubicaine number – a measurement of pseudocholinesterase activity.
    a. Method: application of $1x10^{-5}$ mmol/L dubicaine with benzylcholine to plasma
    b. Results:
        i. Normal plasma cholinesterase activity inhibited 80% → suxamethonium 10min
        ii. Heterozygote abnormality inhibited 40-60% → suxamethonium 30min
        iii. Homozygote activity inhibited 20% → suxamethonium 3-8 hours

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-07A1 Describe the potential adverse effects of administering neostigmine post operatively.

1. Neostigmine is a carbamate quaternary amine anticholinesterase drug.
    a. Post-operative use – reversal of non-depolarising neuromuscular blockade
    b. Dose – 0.05mg/kg IV
    c. Mechanism – neostigmine forms a reversible bond with the esteratic site of AChE → carbylated enzyme complex which is slowly hydrolysed and prevents AChE from hydrolysing ACh → ↑ ACh at NMJ.

2. Adverse effects:
    a. Predicable due to ↑ ACh: neostigmine action is not specific to ACh at the NMJ, and hence ↑ ACh at both nicotinic and muscurinic receptors. Adverse effects are generally muscurinic -
        i. CVS: bradycardia, ↓CO, hypotension large doses
        ii. Resp: Bronchospasm, ↑ secretions
        iii. CNS: minimal – does not cross BBB
        iv. GI: N+V, diarrhoea, cramping, ↑aspiration, ↑ breakdown bowel anastamosis
        v. GU: urinary incontinence
        vi. Other autonomic: lacrimation, salivation, sweating
    b. NMJ effects:
        i. Potentiates phase I neuromuscular blockade by suxamethonium (error)
        ii. High dose: ↑↑ACh at terminal causes a depolarising phase I blockade.
        iii. Re-paralysis: normal intubating doses of NMBD not sufficient to cause relaxation → ↑ dose

3. Treatment adverse effects:
    a. Muscurinic: atropine IV – rapid onset 1min, glycopyrrolate – onset 2-3 min (longer acting, less initial tachycardia)

4. Monitoring reversal
    a. Factors for reversal:
        i. Intensity of block
        ii. Type of NMBD
        iii. Others – drugs, acidosis, electrolytes
    b. Complete recovery: minimal tetanic fade → sustained head lift, hand grip

Ho Medical
ANAESTHESIA

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Pharm-10B5/04B6/01B13/97A12 Briefly describe the pharmacological actions of the anti-cholinesterases with reference to edrophonium, neostigmine and the organophosphorus compounds. Indicate the similarities and differences with the 3 drugs

1. Edrophonium, neostigmine and organophosphates are anticholinesterase agents used for the reversal of neuromuscular blocking drugs.

Property	**Edrophonium**	**Neostigmine**	**Organophosphates**
Physiochemical			
Group	Phenolic quaternary amine	Quaternary amine	Organophosphates – palathion, malathion
Presentation	Clear solution 10mg/mL	Clear solution 2.5mg/mL PO tablet 15-30mg	Multiple
Use	Reversal NMBD Diagnosis MG (Tensilon test) Assess MG crisis	Reversal NMBD Treatment MG Urinary retention	Insecticides Nerve gas Glaucoma (ecothiopate)
Onset	1-2min	7-10min	
Duration	10min	50min	Long – relies on synthesis of new AChE
Dose	0.5mg-1/kg	0.05mg/kg	
Pharmacodynamic			
Mechanism	Reversible weak electrostatic binding to AChE. Quaternary group binds to anionic site, and hydroxyl group binds to esteratic site. ↑ACh release	Reversible covalent bond with esteric site of AChE → carbylated enzyme complex which is hydrolysed at a slow rate (competes with ACh). Hydrolysis regenerates enzyme	Irreversible covalent bond with AChE → phosphorylated complex. Recovery requires synthesis of new enzyme.
CVS	Bradycardia		
Resp	Bronchospasm		
CNS	Nil (not cross BBB)	Nil (not cross BBB) Physostigmine (tertiary) → crosses BBB	Excitation, seizures, ↓IOP, then depression, coma
GI	Diarrhoea, ↑ secretions		
Renal	Urination / incontinence		
Autonomic	DUMBBELSS – diarrhoea, urinary incontinence, miosis, bradycardia, bronchospasm, excitation, lacrimation, salivation, sweating		
Management SEx	Atropine, glycopyrrolate	Atropine, glycopyrrolate	Pralidoxime (reactivate ACh by promoting hydrolysis, early administration - ageing), anti-convulsants, atropine.
Special population			
Pharmacokinetics			
Absorption		Poor PO absorption (hydrophilic), F = 1-2%	Lipid soluble Transcutaneous
Distribution	VD = 1L/kg	VD = 0.5L/kg Protein = 10%	Large VD
Metabolism	Liver: 35% glucoronidation	Plasma: non-specific esterases Liver	
Elimination	Biliary 35% metabolites Renal unchanged 65%	Biliary metabolites Renal unchanged 50%	Long $T_{1/2}$

	$T_{1/2}$ = 110min	$T_{1/2}$ = 77min	

Pharm-07A6/96A10 Briefly outline the acute management of malignant hyperthermia (during a relaxant general anaesthetic). Describe the important aspects of dantrolene pharmacology relevant to treating malignant hyperthermia, including adverse effects.

1. Malignant hyperthermia: a syndrome characterised by hyperpyrexia, muscle rigidity, and hypermetabolism in the context of administration of inhalational anaesthetics and neuromuscular muscle relaxants.
    a. Pathophysiology:
        i. Genetic defect autosomal dominant (1:15000) of the ryanodine receptor in skeletal myocyte.
        ii. Triggers: suxamethonium, volatile anaesthetics
        iii. Ryanodine receptor controls release Ca from SR in response to muscle AP → uncontrolled released Ca^{2+} into myocyte cytoplasm → uncontrolled and excessive contraction
        iv. Hypermetabolic state of skeletal muscle: ↑O_2 consumption, ↑CO_2 production, rigidity, ↑temperature, rhabdomyolysis
    b. Signs:
        i. Musculoskeletal –
            1. Sustained muscle contraction unrelieved by NMBD:
            2. Early sign masseter spasm and trismus
        ii. Metabolic –
            1. Rhabdomyolysis: ↑K^+, ARF, myoglobin release, ↑CK
            2. ↑O_2 consumption: hypoxia, cyanosis
            3. ↑CO_2 production: CO_2 trace, hyperventilation
            4. Fever and sweating
        iii. Cardiac arrhythmias

2. Non-pharmacological management:
    a. Medical support
    b. Cease triggers (volatiles, NMBD) but maintain anaesthesia with non-triggering agents (IV anaesthesia). This may require change of anaesthetic machine/tubing
    c. Airway, Breathing – hyperventilation with O_2
    d. Circulation – aggressive fluid management to avoid
    e. Temperature – cooling < 38 degrees
        i. IV fluids
        ii. Fans
        iii. Sponges
    f. Electrolyte abnormalities:
        i. ↑K^+
    g. Acid-base abnormalities –
        i. associated with lactic acidosis due to anaerobic metabolism in muscle
        ii. Sodium bicarbonate
        iii. Mannitol to prevent ARF

3. Pharmacological management:
    a. Dantrolene: reduced mortality from 90% → 10% since its use.

Property	**Dantrolene**
Physiochemical	
Group	Hydrantoin derivative skeletal muscle relaxant

Formulation	Orange power 20mg in vial, mannitol 3mg,NaOH. pH 9 in water
Isomers	None
Use	Acute malignant hyperthermia Neuroleptic malignant syndrome
Pharmacodynamic	
Dose	IV: 2.5-10mg/kg infusion acute PO: 4-8mg/kg/day prophylaxis for 1-2 days prior to exposure
Onset	
Duration	
Mechanism	Antagonist at sarcoplasmic reticulum ryanodine receptor → ↓ Ca^{2+} release → ↓excitation-contraction → skeletal muscle relaxation, ↓skeletal muscle energy use
Adverse effects	CNS: sedation via ↑GABAergic effects CVS: anti-arrhythmic GIT: reversible hepatic dysfunction GU: mannitol in preparation causes diuresis Muscle: weakness Local: phlebitis
Drug interaction	Ca^{2+} blockers → combination causes ↑ K
Pharmacokinetic	
Absorption	F = 20-70% PO Given IV
Distribution	VD = 0.6L/kg 90% PB
Metabolism	Hepatic metabolism → inactive metabolites
Elimination	Renal excretion $T_{1/2}$ = 10 hours

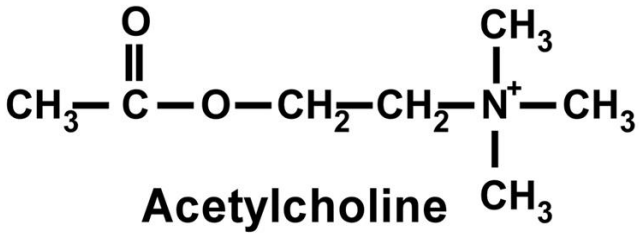
b. Dexamethasone 4mg IV

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

MAKE UP: Outline the structure activity relationships of neuromuscular blocking drugs.

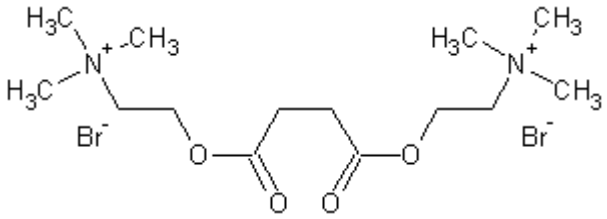
1. Neuromuscular blocking drugs all act by blocking the action of acetyl choline at the nicotinic acetylcholine receptor, at the neuromuscular junction.

2. Acetylcholine:
    a. Acetyl + choline:

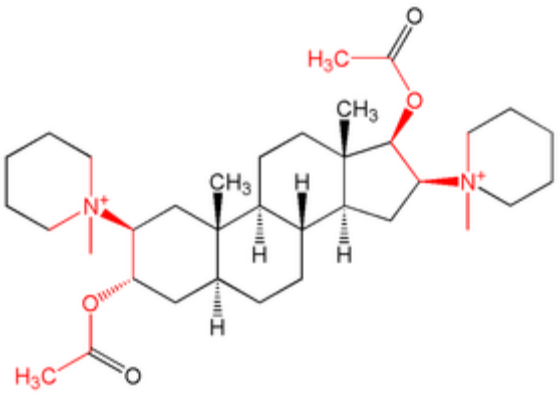


Acetylcholine

    b. Bisquaternary ammonium:
        i. Pharmacokinetic effects:
            1. Water soluble
            2. Distributed to ECF (VD = 0.25L/kg = 14L)
            3. Does not cross BBB, placental barrier
            4. Renally excreted (water solubility)
        ii. Pharmacodynamic effects: action at all acetylcholine receptors
            1. NMJ blockade
            2. Ganglion blockade – autonomic instability
            3. Muscurinic blockade – change in heart rate
            4. Mast cells – histamine release
        iii. Suxamethonium



        iv. Aminosteroids



        v. Benzylisoquinolinium

3. Muscle relaxants:

Group	Structure	Specific properties / problems
Suxamethonium	2 Acetylcholine chains	2nd dose bradycardia

Dr Matthew Ho
BSc(Med) MBBS(Hons) FANZCA

Tubocurarine	Curare	Histamine release
Gallamine		Ganglion blockade, autonomic effects anaphylaxis
Pancuronium	Aminosteroid	1st designer drug – steroid nucleus with two quaternary ammoniums added. Vagolytic – tachycardia and hypotension
Atracurium	Benzylisoquinolinium 10 stereoisomers	Ester hydrolysis (2 laudanosine) + Hoffman reaction (1 laudanosine) 1st drug not renally excreted Histamine release Laudanosine metabolite – CNS toxicity
Cisatracurium	Pure enantiomer	Predominant Hoffman reaction
Vecuronium	Monoquaternary aminosteroid	1st monoquaternary drug (at body pH acts as biquaternary) Less polar – hepatic elimination Bradycardia
Mivacurium	Benzylisoquinolinium	Histamine release Give 3 divided doses
Rocuronium	Monoquaternary aminosteroid	Similar but less potent to vecuronium Relative cardiostability Histamine release