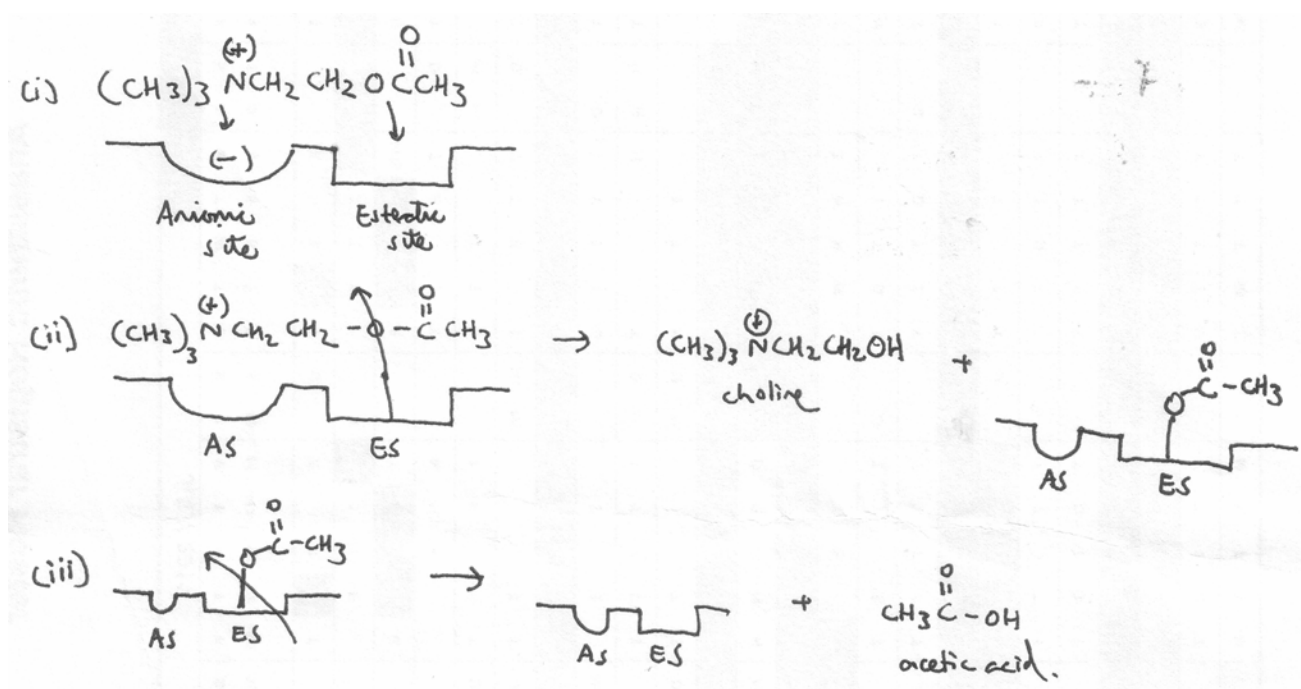


ANTICHOLINESTERASE DRUGS

- (a) *To classify the anti-cholinesterase drugs in relation to mechanism of action.*
- (b) *To compare the contrast the pharmacodynamics and pharmacokinetics of neostigmine, edrophonium, pyridostigmine and physostigmine.*
- (c) *To describe the adverse effects of anticholinesterase agents.*

Anticholinesterase (AChE; aka “True cholinesterase”):

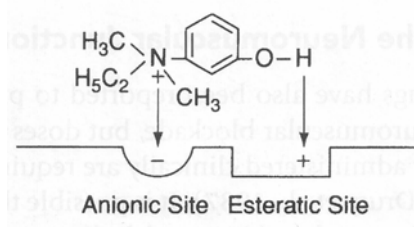
- AChE is found at all synapses involving cholinergic transmission – (i) Nicotinic (NMJ – Troughs of postjunctional fold of MEP, ANS ganglia, adrenal medulla, CNS), and (ii) Muscarinic (PNS post-ganglionic effector cells, sweat glands, CNS)
- It is encoded by a single gene of chromosome 7
- Its main role is to control the duration of ACh receptor activation – It terminates the effect of synaptic ACh by rapidly and efficiently hydrolysing it (Nb. 300k ACh are metabolised per minute such that only 50% of released ACh reaches the target receptor!), thus preventing prolonged receptor activation and target membrane depolarisation
- Structurally, it consists of 6 active sites – Each with an “anionic” and “esteratic” site arranged in a complementary manner to ACh to permit efficient function of the enzyme:
 - (i) Anionic site binds the quaternary nitrogen of ACh (via π -electron charged Glu-residue), which then orients the ester linkage of ACh to the esteratic site
 - (ii) Esteratic site then hydrolyses the ester linkage, leading to the liberation of choline (which is released for reuptake into the presynaptic terminal) and acetylation of the esteratic site
 - (iii) Acetylated esteratic site is later rapidly hydrolyzed to release acetic acid ($t_{1/2} \sim$ microseconds), and thus regenerating the AChE enzyme



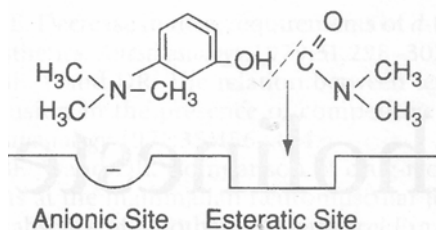
Mechanism of Action of AChEi Drugs:

- (1) Primary effect: Competitive inhibition of AChE
 - AChEi directly competes with ACh binding to AChE, thus resulting in impaired hydrolysis of ACh. This causes an increase in ACh availability in synapses implicated in both nicotinic and muscarinic cholinergic transmission
 - There are three mechanisms of inhibition:

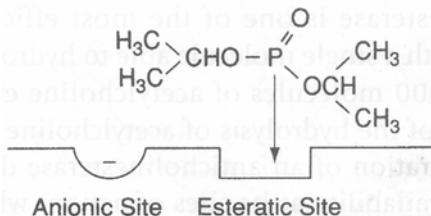
- (i) Reversible inhibition by forming a drug-enzyme complex via non-covalent bonds, such as electrostatic and hydrogen bonds (Edrophonium)
 - Anionic site is bound by quaternary ammonium group of the AChEi via an electrostatic bond, while the esteratic site is bound by a hydroxyl group of the AChEi via a hydrogen bond
 - This drug-AChE complex prevents ACh from binding and being hydrolysed by AChE, BUT the non-covalent bonds allows for easy reversibility!



- (ii) Reversible inhibition by forming a carbamylated enzyme complex with AChE through covalent bonds (Eg. Pyridostigmine, Physostigmine, Neostigmine)
 - Anionic site is bound by quaternary ammonium group of the AChEi via an electrostatic bond, but the esteratic site hydrolyses the AChEi's ester linkage and results in the transfer of a carbamate group to the esteratic site
 - Carbamylated AChE is inactive and cannot bind/hydrolyze ACh until the carbamate-ACh bond dissociates slowly via hydrolysis ($t_{1/2} \sim 15-30$ mins)



- (iii) Irreversible inhibition by forming a drug-enzyme complex through a phosphate-based covalent bond (Eg. Organophosphate-type AChEi – Echothiophate, insecticide (malathion), nerve gas (saran))
 - AChEi forms a stable and inactive drug-enzyme complex by forming a phosphate-based covalent bond with the esteratic site
 - This bond does not undergo hydrolysis, thus return of AChE activity requires synthesis of a new enzyme as spontaneous regeneration of AChE may take a very long time (or never occur!)



(2) Secondary effects:

- (a) Presynaptic effect – AChEi can produce spontaneous contractions of skeletal muscles (fasciculation). Inhibition of AChE leads to increased synaptic ACh, which leads to activation of presynaptic nAChR. This produces a +ve feedback loop on the presynaptic release of ACh onto postsynaptic nAChR
- (b) Direct NMJ effects – At excessive doses of AChEi, NMJ transmission is inhibited due to desensitisation and reduced responsiveness of the MEP to further ACh stimulation.

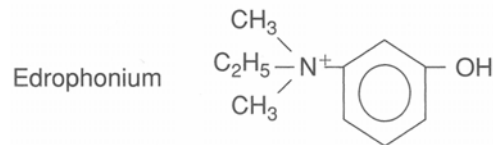
This is the result of excess MEP depolarisation caused by significant levels of ACh in NMJ brought about by AChE inhibition

Classification of AChEi is based upon its mechanism of action:

- (1) Reversible inhibition by forming a drug-enzyme complex through non-covalent bonds (via electrostatic and hydrogen bonds)

- Edrophonium:

- Structure – Quaternary amine; quaternary ammonium compound with a phenol ring (similar to neostigmine, except lacking the carbamate group)



- Presentation – Clear colourless solution of edrophonium chloride (10 mg/mL)
- Pharmacokinetics:
 - Poor lipid solubility (due to quaternary ammonium group) – Does not cross cell membrane barriers (Eg. BBB, GIT, placenta)
 - $V_D \sim 1.1 \text{ L/kg}$
 - Clearance 7-12 mL/min/kg and $t_{1/2} \beta$ 110 mins – Renal elimination unchanged (75%), and hepatic metabolism (25%) into an inactive glucuronidated metabolite that is excreted in bile. Note its effects are prolonged with renal/hepatic failure
- Dose, onset and duration of action:
 - IV 0.5-1 mg/kg (10% potent as neostigmine)
 - Most rapid onset of AChEi (1-2 minutes) – Due to (i) presynaptic site of action (I.e. presynaptic nAChR are activated leading to further ACh release), and (ii) rapid rate of binding to AChEi
 - Historically, short duration of action (10 minutes), UNLESS given at higher clinical doses (when duration of action matches neostigmine)

Note: Lower potency of edrophonium means (i) Less muscarinic side-effects are encountered cf. neostigmine, and that they are easier to prevent with a lower dose of an anticholinergic drug (only half the dose of anticholinergic is given cf. neostigmine), BUT (ii) they are not as effective in reversing intense blocks unless high doses are given (cf. neostigmine)

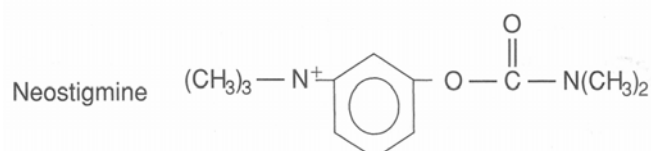
○ Clinical uses:

- (i) Reversal of ND NMBD
- (ii) Diagnosis and assessment of therapy for myasthenia gravis
- (iii) Evaluate presence of dual block with SCh
- (iv) Diagnosis of cardiac arrhythmias

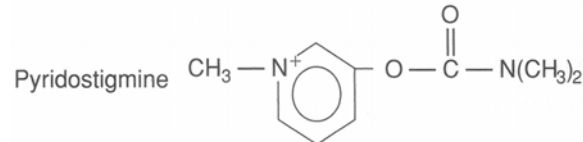
- (2) Reversible inhibition by forming a carbamylated enzyme complex with AChE through covalent bonds

- (a) Neostigmine:

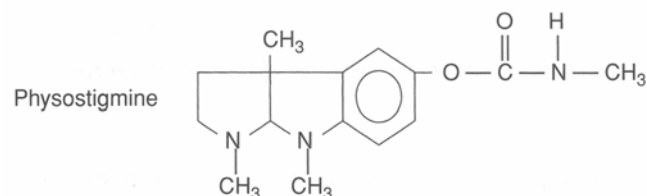
- Structure – Quaternary amine; quaternary ammonium with phenol group esterified to carbamic acid moiety



- Presentation – Clear colourless solution of neostigmine methylsulphate (2.5 mg/mL); 15 mg tablets of neostigmine bromide
- Pharmacokinetics:
 - Poor lipid solubility (due to quaternary ammonium group) – Does not cross cell membrane barriers (Eg. BBB, GIT, placenta)
 - $V_D \sim 0.7$ L/kg; 10% protein-bound
 - Clearance 6-11 mL/min/kg and $t_{1/2} \beta$ 15-80 mins – Renal elimination unchanged (50%); metabolism (50%) by plasma esterases (to quaternary alcohol) and liver enzymes (to active metabolite with 10% activity of parent drug – 3-hydroxyphenyltrimethylammonium). Note its effects are prolonged with renal/hepatic failure
- Dose, onset and duration of action:
 - IV 0.04-0.08 mg/kg; PO 15-50 mg
 - Intermediate onset (onset in 3-5 mins; peak effect in 7-11 mins) – Due to postsynaptic mechanism of action (Ie. Inhibit AChE, leading to more ACh binding to postsynaptic receptors)
 - Duration of action of 40-60 minutes
- Clinical uses:
 - (i) Reversal of ND NMBD
 - (ii) Treatment of myasthenia gravis
 - (iii) Post-operative analgesia (when given intrathecally/epidurally)
 - (iv) Treatment of atonic bladder, paralytic ileus, and/or achalasia (due to increased peristalsis/smooth muscle tone)
- (b) Pyridostigmine:
 - Structure – Quaternary amine; Similar to neostigmine except quaternary ammonium is incorporated into phenol ring



- Presentation – Clear colourless solution of 5 mg/mL; Oral tablets and syrups also
- Pharmacokinetics:
 - Poor lipid solubility (due to quaternary ammonium group) – Does not cross cell membrane barriers (Eg. BBB, GIT, placenta)
 - $V_D \sim 1.1$ L/kg
 - Cleared via renal excretion unchanged (75%) and hepatic metabolism (25%) to an inactive metabolite (3-hydroxy-N-methylpyridinium). Note its effects are prolonged with renal/hepatic failure
- Dose, onset and duration of action:
 - Can be given up to IV 0.4 mg/kg (20% potency as neostigmine)
 - Delayed onset (10-15 mins) – Due to postsynaptic mechanism of action
 - Duration of action > 2 hrs
- Clinical uses:
 - (i) Reversal of ND NMBD
 - (ii) Treatment of myasthenia gravis
- (c) Physostigmine:
 - Structure – Tertiary amine with a carbamate group



- Presentation – Clear colourless solution as 1 mg/mL
 - Pharmacokinetics:
 - Lipid soluble due to tertiary amine – It easily crosses cell membranes (Eg. GIT, BBB, placenta)
 - Cleared mainly by plasma esterases (hydrolyses ester linkage); renal excretion (minor role)
 - Dose, onset and duration of action:
 - IV 0.01-0.03 mg/kg
 - Intermediate onset (5 mins) – Due to postsynaptic mechanism of action
 - Duration of action 1-2 hrs
 - Clinical uses:
 - (i) Treatment of CNS effects of certain drugs (esp central cholinergic syndrome, opioids, anaesthetic agents)
 - (ii) Treatment of anticholinergic overdose
 - (iii) Treatment of post-op shivering
 - Note – It CANNOT be used as reversal agent due to (i) its lipid solubility and CNS penetration, and (ii) the extreme doses required for effect
- (3) Irreversible inhibition by forming a drug-enzyme complex through a phosphate-based covalent bond
- Includes “organophosphate-type” AChEi, which are used to treat glaucoma (Echothiophate), or used as an insecticide (Malathion) or nerve gas (Saran)
 - These agents are tertiary amines and are highly-lipid soluble – Thus easily absorbed via lungs, skin and GIT, and readily crosses BBB to cause marked CNS symptoms. They are also highly associated with risks of AChEi toxicity
 - Since they inhibit AChE irreversibly (via a highly stable phosphate-based covalent bond at the esteratic site of the enzyme), return of AChE function requires de novo synthesis of the enzyme as spontaneous enzyme regeneration may take a long time (or never occur)

Pharmacokinetics of AChEi:

Note – There are very minimal difference in pharmacokinetics between AChEi, thus most differences between them are due to their pharmacodynamics!

- Lipid solubility – AChEi with quaternary ammonium group (edrophonium, neostigmine, pyridostigmine) are poorly lipid soluble and do not cross cell membrane barriers (Eg. BBB, GIT, placenta); Tertiary amines (physostigmine and OP-type AChEi) are lipid soluble and can cross cell membranes easily
- V_D – AChEi generally have a large V_D (0.7-1.4 L/kg) due to extensive tissue storage in organs (esp liver and kidneys), as compared to ND NMBD
- Onset of action – Edrophonium has the most rapid onset (1-2 min) due to its presynaptic effects, while neostigmine, physostigmine and pyridostigmine have more delayed onset due to their postsynaptic mechanism of action
- Duration of action – At clinical doses, they are similar between agents (except for OP's which act indefinitely). This is determined by (i) rate of drug disappearance from the synapse and plasma ($t_{1/2\beta} \sim 60-120$ min), which is influenced by drug dosage, and (ii) Stability of binding to enzyme (or regeneration of AChE), where covalent bonds ($t_{1/2}$ of phosphate bonds $\sim$ indefinite; $t_{1/2}$ of carbamate bonds $\sim 15-30$ mins) last longer than non-covalent bonds (electrostatic/H-bond)

- Clearance (~ 8-16 mL/kg/min) – AChEi are cleared via renal excretion (50-75%) and via hepatic metabolism (25-50%). Note that prolonged action of ND NMBD due to hepatic/renal insufficiency will be matched by prolonged action of AChEi!

Pharmacodynamic Effects of AChEi:

Note:

- Pharmacological effects of AChEi are due to the build up of ACh at both nAChR (NMJ, ANS ganglia including adrenal medulla, CNS) and mAChR (PNS effector cells, sweat glands, CNS)
- However, the muscarinic effects predominate (Eg. bradycardia, secretions, miosis, Etc.) as mAChR are more sensitive than nAChR at a given [ACh] – Thus, when an AChEi is used to reverse a ND NMBD, anticholinergics are administered concurrently to selectively attenuate the unwanted muscarinic effects of AChEi!

- (1) CVS effects
 - o Bradycardia, VEB, heart block and even asystole – Nb. These can occur in transplanted (denervated) heart!
 - o Fall in HR leads to a 2° decreased in CO and MAP
- (2) Respiratory effects
 - o Increased bronchial secretions
 - o Bronchoconstriction
- (3) GIT effects
 - o Increased secretions (increased salivation and production of gastric, intestinal, and pancreatic fluids)
 - o Increased GI motility/peristalsis (causing abdominal cramps, faecal incontinence, and risk of anastomotic leakage – esp with neostigmine)
 - o Increased GI tone (causing increased LOS tone)
 - o Increased PONV
- (4) GUT effects – Increased ureteric tone/peristalsis (causing involuntary micturition)
- (5) Ocular effects
 - o Constriction of iris sphincter (miosis)
 - o Constriction of ciliary muscle (difficult to accommodate or focus near vision)
 - o Decreased IOP (due to increased aqueous humour outflow)
- (6) Increased sweat and lacrimal gland secretions
- (7) MSk effects
 - o At clinical doses, they (a) Antagonise a ND NMBD blockade, but (b) Potentiate a depolarizing block by SCh (due to (i) Increased ACh (promotes ongoing MEP depolarization and desensitisation), and (ii) Inhibition of plasma cholinesterase (ALL AChEi – esp neostigmine and pyridostigmine – EXCEPT edrophonium can inhibit plasma cholinesterase, although not as effectively as it inhibits true cholinesterase))
 - o At high doses, AChEi may – (a) Block NMJ transmission by causing a weak depolarising NMB similar to SCh, where fasciculations and augmented twitch response are seen (due to MEP desensitisation caused by the direct stimulatory effect of excess ACh on it), and (b) Potentiate ND NMBD blockade
 - o Cholinergic crisis (overstimulation of NMJ due to excess ACh) can occur if an AChEi is given to a myasthenic patient who has received a ND NMBD
- (8) CNS effects (ONLY with physostigmine, which can cross the BBB) – Causes diffuse excitation (agitation, confusion, ataxia, seizures)

Clinical Uses of AChEi:

- (1) Reversal of either non-depolarising or phase II depolarising neuromuscular blockade:

- ND NMBDs interfere with normal NMJ transmission by competitive inhibition of ACh binding to and activating nAChR at MEP. Thus, reversing the effects of a ND NMBD by re-establishing normal NMJ transmission involves either:
 - (i) Spontaneous reversal – Agent gradually diffuses away from MEP into plasma, redistributes, and is metabolised and excreted from body
 - (ii) Pharmacological reversal with AChEi (neostigmine, edrophonium, pyridostigmine BUT not physostigmine due to lipid solubility and CNS penetration, and extreme doses required) – These agents indirectly increase the ACh available in the NMJ to bind nAChR (I.e. increase relative ratio of ACh:ND NMBD in NMJ), thus allowing competitive antagonism by ND NMBD to be overcome
- Dosing and timing of AChEi administration:
 - Reversal agents should ALWAYS be given to patients who have received a ND NMBD UNLESS full reversal can be demonstrated or there are post-op plans to continue intubation/ventilation
 - Timing of administration depends on the degree of NMB by a ND NMBD, which is assessed by a peripheral nerve stimulator:
 - AChEi should be given during mild-moderate NMB only (TOF ≥ 3 or single twitch height recovered to $> 10\%$) – This is because AChEi only causes a modest increase in NMJ ACh levels, and thus only enhances the spontaneous recovery of a NMB from a ND NMBD
 - If AChEi is given during a deep ND NMBD block (no tetanic response, TOF count or PTC), the block cannot be reverse as the modest increase in NMJ ACh levels is inadequate to cause recovery
 - Dosing of AChEi:
 - Edrophonium – IV 0.25 mg/kg (if TOF count 4 with minimal fade); 0.5 mg/kg (if TOF count 4 with fade); IV 1 mg/kg IV (if $> 90\%$ twitch depression). Note – Higher doses should be used as it provides faster onset of reversal and prolongs its duration of action (such that it matches neostigmine, and its effect is not outlasted by the NMBD it is reversing!)
 - Neostigmine – IV 0.04 mg/kg (if TOF count ≥ 3); consider maximal dose of IV 0.08 mg/kg for an intense block (TOF count < 3) or incomplete reversal 10 mins after a IV 0.04 mg/kg dose
 - Pyridostigmine – IV 0.2 mg/kg

Note: Once AChEi is maximally inhibited, further administration of AChEi does NOT further antagonize ND NMB – In fact, it can prolong the block! Spontaneously NMJ recovery must be allowed to return (I.e. Wait!)

- The speed and extent of NMB reversal will depend on the following factors:
 - (i) Type of ND NMBD used (which will influence inherent speed of spontaneous recovery)
 - (ii) Pharmacological/physiological factors that may affect ND NMBD duration (Eg. concurrent VA use, ABs, hypothermia, acidosis, electrolyte imbalance, pregnancy, Etc.)
 - (iii) Depth of NMB when reversal initiated (I.e. TOF count)
 - (iv) Type and dose of AChEi given
- Reversal drug needs to be given concurrently with an anticholinergic drug to minimise the unwanted muscarinic ACh effects of AChEi:
 - There are two anticholinergic drugs used – (i) Atropine (onset in 60-90 secs; tertiary amine that can cross BBB and cause central effects such as confusion, drowsiness and CCS), (ii) Glycopyrrolate (slower onset; quaternary amine that cannot cross BBB to cause CNS effects)

- It is ideal to give an anticholinergic drug with a faster onset than AChEi to minimise its muscarinic effects (esp CVS effects, such as bradycardia)
 - Edrophonium – Given with atropine (7-15 mcg/kg) as both have rapid onset. Glycopyrrolate (4-7 mcg/kg) should NOT be given due to risk of bradycardia unless it is administered minutes prior to edrophonium
 - Neostigmine – Can be given with either atropine (50% dose of neostigmine or 20 mcg/kg) or glycopyrrolate (20% dose of neostigmine or 8 mcg/kg) as neostigmine has an intermediate onset of 3-5 mins. Atropine is less favoured due to its faster onset (causes an initial tachycardia which is an issue in patients with CVD) and CNS side-effects
 - Pyridostigmine – Can be given with either atropine (0.1 mg per mg of pyridostigmine) or glycopyrrolate (0.05 mg per mg of pyridostigmine) due to its very slow onset. Both will give initial tachycardia, but glycopyrrolate is preferred due to slower onset
- Determining adequacy and progress of reversal of ND NMBD (I.e. for extubation) can be assessed:

○ (i) Using a peripheral nerve stimulator

Nerve stimulator test	Suggestion of normal NMJ function	Receptor occupancy rate when normal NMJ function is suggested
Single twitch	Qualitatively strong as baseline	75-80%
TOF ratio	Lack of fade (TOFR > 0.7-0.9)	70-75%
DBS	Lack of fade (DBSR > 0.7-0.9)	60-70%
100 Hz/50 Hz sustained tetanus (5 secs)	Lack of fade	70% (50 Hz); 50% (100 Hz)

○ (ii) Clinically

Clinical test	Suggestion of normal NMJ function	Receptor occupancy rate (for ND NMBD) when normal NMJ function is suggested
Tidal volume	TV > 5 mL/kg	80%
Vital capacity	VC > 20 mL/kg	70%
Inspiratory force	P < -40 cmH ₂ O	50%
Head lift	Sustained > 5 secs	50%
Handgrip	Sustained level to baseline	50%

Note: Greater sensitivity of the test is noted by a lower receptor occupancy rate for when normal NMJ function is suggested (I.e. Sustained headlift/hand grip and sustained 100 Hz tetany are the best tests of adequate reversal)

(2) Treatment of CNS effects of certain drugs:

- Due to its ability to cross the BBB, physostigmine can be used to treat:
 - (i) Central anticholinergic syndrome (excess central anticholinergic effects, such as confusion and restlessness, caused by hyoscine >> atropine)
 - (ii) Post-operative CNS effects of anaesthetic agents (esp somnolence and delirium due to VA's and Bz)
 - (iii) Somnolent and respiratory depressive response caused by opioids
- Within the clinical dose range, physostigmine causes unwanted muscarinic side-effects BUT bradycardia generally does not occur – If an anticholinergic is required, glycopyrrolate is preferred as it does not antagonize the CNS effects of physostigmine!!!

(3) Diagnosis, treat, and assess therapy of myasthenia gravis:

- Neostigmine and pyridostigmine are used to treat myasthenia gravis by increasing NMJ levels of ACh, thereby increasing skeletal muscle responsiveness to repetitive stimuli –

Limited oral bioavailability (2° to poor lipid solubility), and requires an anticholinergic agent to be given concurrent to minimise muscarinic side-effects

- Edrophonium is used to (i) diagnose myasthenia gravis (as part of Tensilon test), and (ii) assess AChEi drug therapy (Drug therapy is inadequate/myasthenic crisis is evidence if symptoms subside after IV edrophonium is given; Drug therapy is excessive if cholinergic crisis ensues after IV edrophonium is given)

(4) Treatment of glaucoma – Topical AChEi (echothiophate) is used to decrease IOP

(5) Post-operative analgesia

- Intrathecal or epidural neostigmine (50-100 mcg) can be used for postoperative analgesia or chronic pain therapy – Mechanism involves inhibiting breakdown of spinal ACh, which is increased in pain states
- However, there are issues with PONV, pruritus, faecal incontinence, atropine-resistant bradycardia (at high doses) and prolonged sensory/motor block

(6) Post-operative shivering – Can be managed with physostigmine

(7) Diagnosis of cardiac arrhythmias – Edrophonium can be used to diagnose SVT (incl WPW syndrome)

(8) Treatment of paralytic ileus or atonic bladder (only neostigmine)

(d) *To outline the effects and treatment of poisoning with organophosphate compounds.*

AChEi overdose:

- Organophosphate-type AChEi (Eg. Insecticides) are a common cause of AChEi overdose as they are easily absorbed via the lungs, skin and GIT due to their high lipid-solubility (due to tertiary amine structure). Moreover, they also cause more CNS symptoms as they can cross the BBB
- Symptoms of AChEi overdose symptoms are due to excessive:
 - o (i) Muscarinic effects – Difficult to focus vision, excess salivation, bronchoconstriction, respiratory secretions, bradycardia, abdominal cramps, N/V, sweating, and loss of bladder/rectal control
 - o (ii) Nicotinic effects – Muscle weakness leading to paralysis with apnoea, fasciculations, hypertension and tachycardia
 - o (iii) CNS effects (esp if AChEi is lipid-soluble agent, such as OP's) – Confusion, ataxia, seizures, coma, and respiratory depression
- Management includes:
 - o (1) Atropine – Treats muscarinic symptoms by antagonising effect of ACh on mAChR. Requires repeated dosing until symptoms disappear
 - o (2) Pralidoxime
 - “AChE reactivator” that promotes hydrolysis of the covalent bond that the drug has with the enzyme (esp drugs that phosphorylate AChE, rather than those that carbamylate it)
 - Treats both muscarinic and nicotinic symptoms by reducing synaptic levels of ACh through reactivation of AChE
 - Ineffective unless given within minutes of exposure to AChEi. Requires repeated dosing until symptoms disappear
 - o (3) Supportive therapy (Eg. ETT/mechanical ventilation, seizure control, circulatory management with IVF, Etc.)

Aside: Sugammadex

Structure of sugammadex:

- Cyclodextrin moiety – Circular arrangements of oligosaccharides with extra sugar molecules for specific affinity to rocuronium

Mechanism of action of sugammadex:

- Forms tight 1:1 complex with ND NMBD (mainly aminosteroids) via intermolecular bonds (van der Waal forces and H-bonding) – NOT covalent bonds
- This creates a large [] gradient for the ND NMBD to diffuse from the NMJ into plasma, thereby allowing residual NMJ ACh to overcome the competitive inhibition of nAChR and for normal NMJ function to return
- Sugammadex-ND NMBD complexes are then renally excreted

Pharmacokinetics of sugammadex:

- Nil protein binding and Vd 15 L/kg
- Clearance 91 mL/min and $t_{1/2\beta}$ 130 mins – Mainly renally excreted unchanged (90%), thus it is not recommended for use with severe renal impairment as it accumulates and its duration of action is prolonged. It is NOT metabolised in the body

Clinical uses of sugammadex:

- Reversal agent for aminosteroid ND NMBD – Specifically rocuronium, but will also bind vecuronium (weakly) and pancuronium (very weakly) – that is used in three situations:
 - o (1) Unexpected residual block or incomplete reversal with neostigmine (Eg. obese patients, prolonged block due to various physiological/pharmacological factors)
 - o (2) Reversal of deep block (Eg. unexpected early end to surgery; reverse block by rocuronium during modified RSI in CVCI situation as the patient has contraindications to SCh)
 - o (3) Reversal of routine block
- Note that sugammadex has NIL innate biological activity

Dosing of sugammadex:

- Dosing is dependent on the depth of block:
 - o (i) Immediate reversal with no response on nerve stimulator (Ie. post modified RSI with rocuronium) – 16 mg/kg (1.5 mins to achieve TOFR 0.9)
 - o (ii) Deep block (PTC 1-2) – 4 mg/kg (3 mins to achieve TOFR 0.9)
 - o (iii) Routine/partial block (TOFC 2) – 2 mg/kg (2 mins to achieve TOFR 0.9)

Issues with sugammadex use:

- (1) Inability to reuse rocuronium post-sugammadex
 - o If a standard rocuronium dose is being given post-sugammadex use, need to wait 6 hrs (if 2mg/kg given), 8 hrs (if 4 mg/kg given), and 12 hrs (if 16 mg/kg was given)
 - o If a modified RSI rocuronium dose is being given post-sugammadex use, need to wait 2 hrs (if 4 mg/kg given) and 6 hrs (if 16 mg/kg was given). No wait time needed if 2 mg/kg was used
 - o Otherwise, consider using a benzylisoquinoline ND NMBD
- (2) Allergy to rocuronium (and other aminosteroid ND NMBD) – Note that there have been NO allergies to sugammadex thus far!
- (3) Cost of sugammadex
- (4) Sugammadex does NOT work with benzylisoquinoline ND NMBDs