ANTICHOLINERGIC DRUGS

(a) ***To describe the pharmacology of acetylcholine and muscarinic and nicotinic receptors.***

Pharmacology of Acetylcholine:

- ACh is the neurotransmitter for the:
  - (1) Entire parasympathetic NS (PNS ganglia and effector cells)
  - (2) Parts of sympathetic NS (SNS ganglia, adrenal medulla, sweat glands)
  - (3) Parts of CNS
  - (4) Somatic nerves innervating skeletal muscle (NMJ)
- Its pharmacology (synthesis, storage, release, mechanism of action, and metabolism) is noted in "Neuromuscular blocking agents" and "Anticholinesterase drugs"

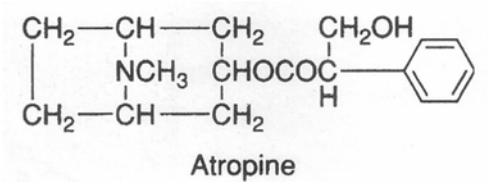
Pharmacology of Muscarinic and Nicotinic Receptors:

Receptor type	Receptor subtype	Location	MOA	Effect
Nicotinic (nAChR)	N1	Pre and post-synaptic	Receptor-linked ion channel (pentameric) → ACh binds to each α-subunit opens channel → ↑ Na^+ influx >> K^+ efflux → depolarisation	NMJ - Post-synaptic: Junctional and extrajunctional receptors → skeletal muscle contraction - Presynaptic: Prejunctional → +ve feedback on presynaptic ACh release
	N2	Post-synaptic		- ANS ganglia and adrenal medulla → efferent transmission of SNS and PNS and Adr release - CNS
Muscarinic (mAChR)	M1	Post-synaptic	Gq	- CNS - Gastric parietal cell → gastric acid secretion
	M2	Post-synaptic	Gi	- Heart (SAN and AVN) → -ve chronotropy - Bronchial SM → bronchoconstriction - CNS
	M3	Post-synaptic	Gq	- CNS - Glandular tissue (lacrimal, salivary, GI, GU, respiratory and sweat glands) → ↑ secretions - Bronchial SM → bronchoconstriction - Vascular SM → vasodilation (via NO release) - GI and GU SM contraction of walls; relaxation of sphincters - Uterine contraction - Penile erection - Iris and ciliary muscle contraction
	M4	Post-synaptic	Gi	Unknown
	M5	Post-synaptic	Gq	Unknown

(b) ***To compare and contrast the pharmacodynamics and pharmacokinetics of atropine, hyoscine and glycopyrrolate.***

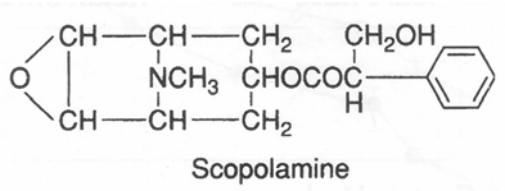
Structure of anticholinergic drugs:

- Anticholinergic drugs are esters of an "aromatic acid" combined with an "organic base". Note that the (i) ester link and (ii) cationic components are vital for binding to mAChR
    - (1) Atropine – Naturally-occurring alkaloid of belladonna plant. Tertiary amine that is an ester of tropic acid (aromatic acid) and tropine (organic base). Exists as a racemic mixture of D- and L-isomers but only L-isomer is active. Lipid soluble and can cross BBB (CNS/ocular effects) and placenta



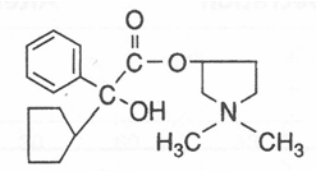
Atropine

    - (2) Hyoscine (scopolamine) – Similar structure as atropine, but the organic base is scopine ("O" bridge incorporated into tropine to form scopine). Like atropine, it is a naturally-occurring alkaloid of belladonna plant, a lipid-soluble tertiary amine, and exists as a racemic mixture with only the L-isomer being active



Scopolamine

    - (3) Glycopyrrolate – Synthetic congener of belladonna alkaloid. Quaternary ammonium containing mandelic acid (aromatic acid). Lipid-insoluble (due to quaternary ammonium), and thus cannot cross BBB (nil CNS/ocular effects) or placenta. However, it has more potent peripheral effects!



Glycopyrrolate

Mechanism of action of anticholinergic drugs:

- Selectively and competitively inhibit ACh binding to and activating mAChR at postganglionic cholinergic sites (Ie. Parasympatholytic or antimuscarinic activity) – Note that it affects all types of mAChR indiscriminately
- It has minimal to no effect at nAChR, UNLESS at excessively high doses
- Its effects can be reversed by increasing the relative [ACh] in synapse to relative [ ] of the anticholinergic drug

Pharmacodynamic effects of anticholinergic drugs:

- CVS effects:
    - Tachycardia (with 2° rise in C.O. but not MAP) due to inhibition of M2R in SA node (ideal in treating vagal-induced bradycardias due to BRR, peritoneal stimulation, oculocardiac reflex)
    - At low doses, transient slowing of HR can occur due to (i) weak peripheral agonist effect at M2R, (ii) inhibition of presynaptic M1R on vagus nerve endings

(this blocks the –ve feedback on further ACh release, which leads to increased M2R stimulation at the SA node), and/or (iii) central vagal nucleus effect
    - Decreased heart block, but increased atrial arrhythmias and nodal (junctional) rhythms due to facilitation of AV nodal conduction

> Note that anticholinergics have NO effect on HR for a denervated heart

    - Little effect on PVR and cardiac contractility (due to paucity in mAChR there), but large doses can cause peripheral vasodilation ("atropine flush")
    - Increased sympathomimetic activity due to inhibition of presynaptic mAChR on Adr nerve terminals (which normally inhibits NAd release)
- Respiratory effects:
    - Inhibit respiratory tract mucosa secretions (ideal as a premed to reduce secretions caused by irritating VAs, such as ether)
    - Bronchodilation (and increased anatomic DS) due to bronchial SM relaxation
- CNS and ocular effects:
    - Stimulation (excitation, restlessness, hallucinations) or depression (sedation, amnesia)
    - Mydriasis (pupil dilation) and cycloplegia (inability to accommodate to near-vision)
- GIT effects:
    - Decreased salivary secretions and gastric secretions (only at high doses)
    - Decreased GI motility (delayed gastric emptying, reduced intestinal motility/peristalsis)
    - Reduced LOS tone (possible increased risk of aspiration)
    - Anti-emetic (via a central mechanism)
- GUT effect – Decreased ureteric/bladder tone (risk of urinary retention)
- Other – Reduced sweating (causing increased body temp and "atropine fever")

<u>Types of anticholinergic drugs: Atropine, Hyoscine, Glycopyrrolate</u>

(1) <u>Atropine</u>:
- Presentation – Clear and colourless solution of atropine sulphate (1.2 mg/mL or 600 mcg/mL); 600 mcg tablets
- Pharmacokinetics:
    - Usually given IV/IM (oral bioavailability 10-25% only despite lipid solubility)
    - Lipid-soluble (as tertiary amine) and readily cross BBB, eyes and placenta
    - 50% protein bound. Vd 2-4 L/kg
    - Clearance 70 L/hr and t ½ β 2.5 hrs – Extensive hepatic esterase metabolism to tropine/tropic acid (80%). Minimal renal excretion unchanged (20%)
- Onset/duration of action and doses:
    - When given IV, it has an onset of 60 seconds with duration of action of 30-60 minutes
    - Premedication: IV or IM 10-20 mcg/kg (up to 0.6 mg) or PO 0.2-0.6 mg
    - Treatment of vagal-induced bradycardias and asystolic/PEA cardiac arrests: IV 15-70 mcg/kg (up to IV 2-3 mg for complete cardiac vagal blockade)
    - As part of ND NMBD reversal: IV 20 mcg/kg (with neostigmine), 7-15 mcg/kg (with edrophonium), 0.1 mg per mg pyridostigmine
- Clinical uses/issues:
    - (a) Premedication for sedation/antisialogogue effect
        - Compared with hyoscine, its antisialogogue and anti-respiratory tract secretion effects were less effective (due to reduced potency) and is associated with more CVS side-effects (Eg. Tachycardia)

        - However, at clinical doses the CNS effects are minimal (mainly sedation and mild post-operative cognitive deficits). Less likely to cause CCS cf. hyoscine
        - Nb. Was previously used as a premed against cardiac vagal reflexes and respiratory tract secretions for when VAs (esp ether) were very irritating
    - (b) Potent cardiac and respiratory effects:
        - Ideal in treating reflex vagal-induced bradyarrhythmias (due to BRR, peritoneal stimulation, oculocardiac reflex) due to more rapid onset and effect – Issues: (i) Tachycardia is a concern in those with IHD, (ii) Initial bradycardia if small doses given, (iii) Lacks effects on denervated (transplanted) hearts
        - Used in asystolic/PEA cardiac arrests
        - Useful for treating acute COPD/asthma – Causes significant bronchodilation and reduces AW secretions (can be nebulised to prevent unwanted systemic effects (esp CVS))
    - (c) Antagonise PNS effects of AChEi during reversal of ND NMBD
        - Fast onset ideal for edrophonium (and possibly neostigmine), but not pyridostigmine
        - Issues – (i) Unwanted CNS and ocular effects, (ii) Inhibits PNS longer than glycopyrrolate (poses a problem in patients with CVS disease)
    - (d) Treatment of hiccups with LMA placement (IV 0.5 mg)
    - (e) Risk of urinary retention (esp in pts with bladder neck obstruction, BPH)
    - (f) Cautious use in patients with glaucoma (topical atropine – NOT IV/IM – can occlude angular space and obstruct venous drainage of intraocular fluid, leading to raised IOP)

(2) <u>Hyoscine (Scopolamine)</u>:

- Presentation – Clear and colourless solution of hyoscine hydrobromide (0.3, 0.4, 1 mg/mL); also as a transdermal patch 0.5 mg or tablet (10 mg)
- Pharmacokinetics:
    - Usually given IV, IM, transdermally (oral bioavailability 10-50% only despite lipid solubility)
    - Lipid-soluble (as tertiary amine) and readily cross BBB, eyes and placenta
    - 10% protein bound. Vd 2 L/kg
    - Clearance 45 L/hr and t ½ β 2.5 hrs – Extensive hepatic esterase metabolism to scopine/scopic acid (99%). Minimal renal excretion unchanged (1%)
- Onset/duration of action and doses:
    - Duration of action is shorter than atropine
    - Premedication: IM 10-20 mcg/kg; PO 20 mg q6h
- Clinical Uses/Issues:

> Most clinical effects of hyoscine are derived from its CNS/ocular effects (sedation, amnesia, antiemetic, mydriasis, antisialogogue) as it is highly lipid-soluble and crosses the BBB. It has far less peripheral effects (cardiac and respiratory)

    - (a) Ideal premedication for sedation and reducing salivation/respiratory secretions (preferred over atropine) due to:
        - More antisialagogue effects/anti-respiratory secretions (2-3x more potent) and far less CVS side-effects
        - More CNS effects (esp sedation and amnesia; 100x more potent than atropine) BUT increased risk of CCS/delayed awakening from GA
    - (b) Prevents (and also treats) motion-induced N/V and PONV – Best used as a transdermal patch (to minimise side-effects with IV/oral forms) and prophylactically
    - (c) Potent antispasmodic of GIT/biliary tree

        - (d) Avoided in patients with closed-angle glaucoma (more potent eye effects than atropine)
        - (e) Treat reflex vagal-mediated bradycardia and acute asthma/COPD – BUT not as ideal as atropine due to slower onset and lower efficacy

(3) Glycopyrrolate:
- Presentation – Clear and colourless solution (0.2 mg/mL)
- Pharmacokinetics:
    - Given IM/IV (not PO due to 5% oral bioavailability and poor lipid solubility)
    - Lipid-insoluble (due to quaternary ammonium) and does not cross BBB, eyes or placenta
    - Clearance 0.9 L/hr and t ½ β 1.2 hrs – 80% excreted in urine unchanged (thus accumulates in presence of renal failure). Minimally metabolised (20%)
- Onset/duration of action and doses:
    - Onset in 2-3 minutes with similar duration of action as atropine when given IV
    - Doses are generally half that of atropine:
        - (i) Premedication: IV 5-10 mcg/kg (up to 0.3 mg)
        - (ii) As part of ND NMBD reversal: IV 8 mcg/kg (with neostigmine), 4-7 mcg/kg (with edrophonium), 0.05 mg per mg pyridostigmine
- Clinical Uses/Issues:

> Nil CNS (such as sedation, amnesia, CCS), ophthalmic effects (such as raised IOP from mydriasis/cycloplegia), and placental transfer due to poor lipid solubility (from quaternary ammonium group)

    - (a) Premedication for antisialogogue/anti-respiratory secretion effects
        - Potent inhibition of salivation and respiratory tract secretions (2x more potent than atropine)
        - Lacks CNS effects (sedation, amnesia, CCS) and less CVS effects
    - (b) Treat reflex vagal-induced bradyarrhythmias – BUT not as fast onset or as effective as atropine
    - (c) Antagonise PNS effects of AChEi during reversal of ND NMBD
        - Slower onset ideal for neostigmine and pyridostigmine
        - Ideal for patients with CVS issues (MI, arrthythmias) due to shorter impairment of PNS activity. Also devoid of CNS/ocular effects
    - (d) Treatment of acute asthma/COPD – Bronchodilator effect similar to atropine
    - (e) Reduce gastric acidity and increase GI motility – BUT high doses required and risk of side-effects from other muscarinic effects)
    - (f) Chemically incompatible with STP and diazepam

(c) ***To describe the effects of overdosage of anti-cholinergic drugs and its management.***

Central Cholinergic Syndrome (CCS):

- Occurs when there is an overdose of a lipid-soluble anticholinergic drug (mainly tertiary amines – hyoscine >> atropine; not glycopyrrolate due to its quaternary ammonium) that crosses the BBB and causes overwhelming competitive inhibition of mAChR in the CNS
- CNS symptoms include – Sedation (leading to unconsciousness), amnesia, hallucinations, agitation/excitement, ataxia and delirium. Often mistaken as "delayed recovery from GA"
- Managed with an AChEi that can penetrate BBB and increase the ACh levels in the CNS – Only physostigmine (lipid-soluble tertiary amine) can be given (doses of 15-60 mcg/kg q1-2 hrs due to its rapid metabolism). The other AChEi (edrophonium, neostigmine, pyridostigmine) all contain quaternary ammonium and thus cannot cross the BBB

Anticholinergic drug overdose:

- Overdose of an anticholinergic drug leads to symptoms of overwhelming mAChR blockade (Nb. "hot as a hare, dry as a bone, red as a beet, blind as a bat, mad as a hatter"):
    - Reduced salivation leading to dry mouth and dysphagia
    - Blurred vision and photophobia
    - Tachycardia
    - Increased MV (from bronchodilation)
    - Skin is dry and flushed (esp face, neck, chest)
    - Increased body temperature ("Atropine fever")
    - CNS symptoms range from CCS to seizures, coma and respiratory depression
- With excessive overdose, symptoms of nAChR blockade are apparent – Skeletal muscle weakness and orthostatic hypotension
- Managed with AChEi that increase ACh levels at mAChR BOTH centrally and peripherally (and also at nAChR) – Thus, physostigmine is used again (15-60 mcg/kg IV q1-2 hrs due to rapid metabolism)