ANTICHOLINERGIC DRUGS

Introduction

- Drugs which **block** ***Cholinoreceptors*** have important clinical effects, some of which are of great clinical value

- **Muscarinic** and **Nicotinic**
  - M_1, M_2, M_3, M_4 and M_5
  - N_N and N_M

CHOLINERGIC RECEPTORS

- **Conventionally –** Anticholinergic drugs are those which block actions of Ach autonomic effectors and I the CNS exerted through Muscarinic receptors
- Nicotinic (N_N) antagonists – ganglion blockers

N_M Blockers – neuromuscular blockers

- **Atropine** is the prototype – many synthetic and semi synthetics are available now
- All are **competitive antagonists**

CLASSIFICATION – ANTICHOLINERGIC DRUGS

I. **Natural:** Atropine and Hyoscine (scopolamine)

II. **Semisynthetic derivatives:** Homatropine, Atropine methonitrate, Hyoscine butylbromide, Ipratropium bromide, Tiotropium bromide

III. **Synthetic Compounds:**

(a) **Mydriatics:** Cyclopentolate and Tropicamide

(b) **Antisecretory-antispasmodics:**

Quartenary ammonium compounds: Propantheline, Oxyphenonium, Clidinium, Pipenzolate methylbromide, Glycopyrrolate, Isopropamide

Tertiary amines: Dicyclomine, Valethamate, Pirenzepine

(c) **Vasicoselective:** Oxybutynin, Flvoxate, Tolterodine

(d) **Antiprkinsonian:** Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden

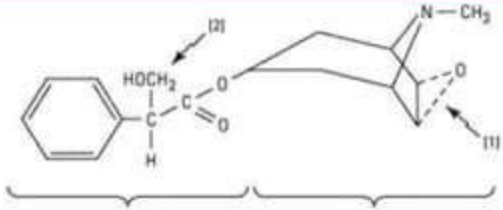
IV. Additionally – TCAs, Phenothiazines and Antihistaminics

Atropine as Prototype

- **Atropine (hyoscyamine**) is found in the plant *Atropa belladonna*, or deadly nightshade
- Also in Datura stramonium, also known as jimsonweed (Jamestown weed) or thorn apple
- **Scopolamine (hyoscine)** occurs in *Hyoscyamus niger*

ATROPINE - CHEMISTRY

- **Atropine:** Ester of **tropic acid (aromatic acid) + tropine**
- **Scopolamine:** Ester of **tropic acid (aromatic acid) + scopine**
- Chemically tropine and scopine are closely similar
- Most of the actions of both are similar



The structure of atropine (oxygen at *[1]* is missing) or scopolamine (oxygen present). In homatropine, the hydroxymethyl at *[2]* is replaced by a hydroxyl group, and the oxygen at *[1]* is absent.

Atropine – Mechanism of Action

- Atropine causes reversible (surmountable) blockade of cholinomimetic actions at muscarinic receptors
  - blockade by a small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist
- Atropine is highly selective for muscarinic receptors
- Does not distinguish between the M1, M2, and M3
- Some quaternary amine antimuscarinic agents have significant ganglion-blocking actions

Atropine - Pharmacokinetics

- **Absorption:**
  - The natural alkaloids and most tertiary antimuscarinic drugs are well absorbed from the gut and conjunctiva – some even over the skin (scopolamine)
  - Penetrates cornea freely
  - Quaternary ones – only upto 30%
- **Distribution:**
  - Atropine and the other tertiary agents are widely distributed in the body
  - Scopolamine is rapidly and fully distributed into the central nervous system where it has greater effects than most other antimuscarinic drugs
  - Quaternary derivatives are poorly taken up by the brain
- **Metabolism:**
  - Atropine is metabolized in liver by conjugation and 60% excretes unchanged in urine
  - Effects disappear quickly within 2 Hrs except eye
  - Hyoscine is more completely metabolized
- **Preparations:** Atropine IM or IV; Hyoscine – Oral/IM/transdermal

PHARMACOLOGICAL ACTIONS - CNS

- **Overall CNS stimulant**
- At low dose - Atropine has only peripheral effects and minimal stimulant effect on CNS – low entry
- Scopolamine has more marked central effects (depressant) – amnesia and drowsiness.
- Atropine stimulates many medullary centres – **vagal, respiratory** and **vasomotor.**
- Depresses vestibular excitation – antimotion sickness property.
- Blocks basal ganglia cholinergic over activity – blocks tremor, rigidity

PHARMACOLOGICAL ACTIONS OF ATROPINE - CVS

- **Heart:** Moderate and high doses: TACHYCARDIA (Blockade of M2 receptor on SA node - vagal tone decreases HR)
- Higher the vagal tone – more Bradycardia - in young adults
- AVN – Atropine abbreviates refractory period of AVN– facilitates AV conduction rate (reduced PR interval in ECG)
- **IM/SC injection initially –** transient **BRADYCARDIA** – may be due to inhibition of prejunctional postsynaptic M1 autoreceptor inhibition (not due to stimulation of vagal centre)
- Evidenced by Pirenzepine (selective M1 blocker) injection does not cross BBB
- **BP: No consistent effect** – tachycardia and VMC stimulation – raises BP; but histamine release and direct vasodilator action counteract

PHARMACOLOGICAL ACTIONS, ATROPINE-EYE

- **MYDRIASIS**
- Topical atropine and other antimuscarinic drugs - results in unopposed sympathetic dilator activity and **mydriasis**
- **Cycloplegia** and **abolition of light reflex** - desirable in Ophthalmology
- Photophobia and blurring of near vision
- **IOP** rises: hazardous in narrow angle glaucoma
- Dry Eye: Not desirable

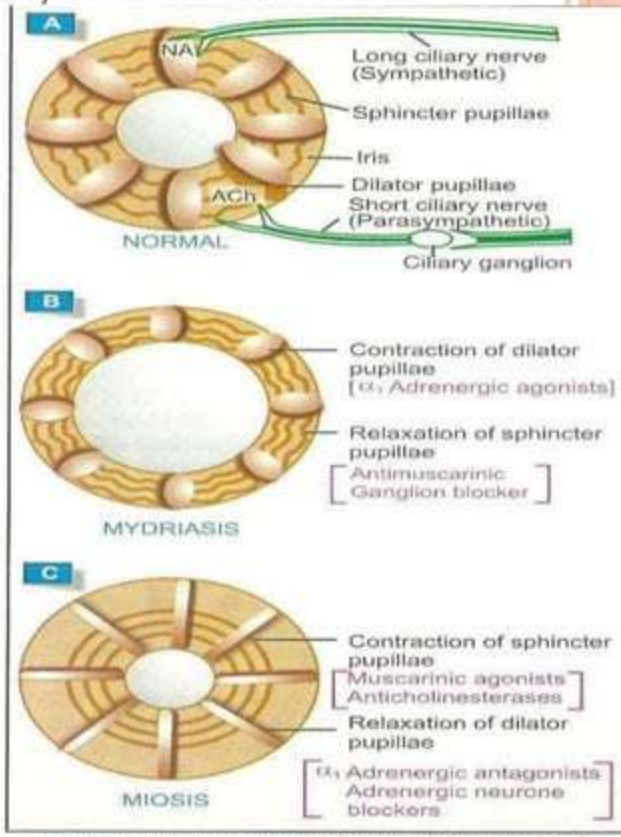


Fig. 8.1: Autonomic control of pupil (A); and site of action of mydriatics (B) and miotics (C)

Atropine on Smooth Muscle

- **Respiratory:** Bronchodilatation and reduction in airway resistance – COPD and asthma patients
- **Urinary:** Relaxation of ureter & bladder – urinary retention in older males with BHP
  - Sometimes useful in increasing bladder capacity and controlling detrussor hyperreflexia - neurogenic bladder/enuresis
- **Visceral SM:** Relaxation – mediated by M3 blockade
  - Tone and amplitude of contraction of Stomach and Intestine reduced
    - Passage of chyme reduced – **CONSTIPATON** and relieve of **SPASM**
  - But, less peristalsis suppression – ENS
  - More effective to exogenous ACh administration

Atropine on Glands

- Decreases salivary, sweat, tracheobronchial and lachrymal secretions (M_3 blockade)
  - dryness of mouth, dry skin and conjunctiva and difficulty in talking and swallowing
- Stomach (M_1): decreases acid, pepsin and mucus secretions – pH of gastric contents may increase – in empty stomach
- But pH not interfered– as also decreases bicarbonate (HCO_3) secretion – **Higher doses required** to cause acidity
- Atropine is less efficacious than H_2 blockers
- No effect on intestinal and pancreatic secretion
- No effect on bile production

PHARMACOLOGICAL ACTIONS OF ATROPINE – CONTD.

- **Temperature:** Increases – decrease sweating + stimulation of temperature regulating centre in hypothalumus
- **Local anaesthetic action:** on cornea
- Sensitivity of organs – Saliva, sweat, bronchial secretion > smooth muscle of intestine and bladder > gastric gland and smooth muscle

Semi synthetics and Synthetics

ATROPINE SUBSTITUTES

Atropine Substitutes

- Semisynthetic: Mydriatic, antispasmodic, bronchodilator etc.
- Synthetic: Mydriatic, antisecretory-antispasmodic (quaternary - antisecretory or tertiary), vasicoselective, antiparkinsoian
- Quaternary compounds (for peripheral action only in GIT):
  - Incomplete oral absorption
  - Poor CNS and eye penetration
  - Slow elimination – longer acting
  - Higher Nicotinic blocking property – postural hypotension and impotence
  - Neuromuscular blockade at higher doses

INDIVIDUAL DRUGS – ATROPINE SUBSTITUTES - SEMISYNTHETIC

- Hyoscine Butylbromide: Oesophageal and GIT spastic conditions – Buscopan – Oral/IM
- Atropine methonitrate: Abdominal colics and hypercidity – Oral/IM
- Ipratropium Bromide: Selective action on Bronchial SM - dilatation
  - Does not alter volume and cosistency of respiratory secretion
  - Enhanced mucocilliary clearance (contrast to Atropine)
  - Slowly acting (slow onset and late peak) Bronchodilator - 1-2 Hrs (prophylactic use) – contrast to sympathomimetics – 4-6 Hrs
  - Acts mainly on larger Central airways (contrast to sympathomimetics)
  - More effective in COPD than Asthma
  - ADRs: cough, bad taste and nervousness – rare systemic effects
- Tiotropium bromide: Ipratropium congener – longer acting and more M_1/M_3 selective

Atropine substitutes – Quaternary

- Propantheline: Used in peptic ulcer and gastritis – reduces gastric acid secretion – mild side effects – not popular now
- Oxyphenonium: Peptic ulcer and gastric hypermotility
- Clinidium: Nervous dyspepsia, gastritis, IBS, colic etc.
- Pipenzolate methyl bromide: Flatulent dyspepsia, infantile colics
- Glycopyrrolate: IM/oral – rapid acting without central effects – preanaesthetic medication

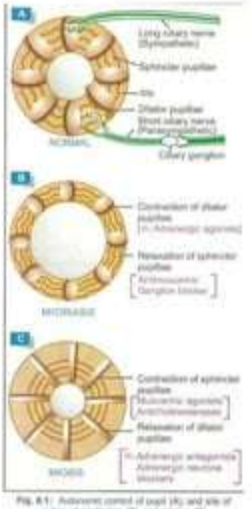
Atropine substitutes – Tertiary Amines

- **Dicyclomine , valethamate** and **Pirenzepine**
- Dicyclomine: Direct SM relaxant and antispasmodic – weak anticholinergic
  - Lesser side effects than Atropine
  - Also antiemetic – morning sickness
  - Atropine toxicity in infants (not recommended below 6 months)
  - Dysmenorrhoea and IBS
- Valethmate: Dilatation of Cervix in delayed labour (visceral antispasmodic)
- Pirenzepine: Selective M_1 antagonist – no action on M_2 and M_3 (no atropinic side effects)
  - Decreases gastric acid secretion - promotes ulcer hea
  - Less popular now

ATROPINE SUBSTITUTES
- VASICOSELECTIVE – CONTD.

- **Oxybutynin:**
  - Specific selectivity for receptors in Urinary bladder and salivary gland (M_1/M_3)
  - Additional smooth muscle relaxation property and local anaesthetic property
  - Uses
    - Detrussor instability – urinary frequency and incontinence
    - Spina bifida and nocturnal enuresis
    - Involuntary voiding in patients with neurologic disease - children with meningomyelocele
    - Bladder surgery - urologic surgery
    - Dose: 5 mg BD/tds or local instillation
- Tolterodine – M_3 selective–overactive bladder with urinary urgency
- Flavoxate – similar to Oxybutynin
- **Drotaverine:** Non anticholinergic smooth muscle relaxant – inhibition of PDE-4 - elevation of cAMP/cGMP – sm relaxation
  - Renal colic, biliary colic, IBS, uterine spasms etc.
  - No anticholinergic side effects - Dose: 40 – 80 mg tds

ATROPINE SUBSTITUTES - MYDRIATICS



- Atropine: Slow and long lasting
  - Onset of action: 30 – 40 minutes
  - Cycloplegia: 1 – 3 Hours
  - Duration of action: 7 – 10 days

	Homatropine	Cyclopentolate	Tropicamide
Potency	10 times less	Potent	Less reliable
Onset of action	45 – 60 min	30 – 60 min	20 – 40 min
Duration of action	1 – 3 days and 1-2 days	1 day	3 – 6 Hours
Children use	Unsatisfactory cycloplegia	Behavioural abnormality	Mental and mood changes

ATROPINE: THERAPEUTIC USES - ANTISECRETORY

1. Preanaesthetic medication: atropine, hyoscine and glycopyrrolate etc.
   - Defn.: Refers to use of drugs before anaesthesia to make it more pleasant and safe
   - Irritant GA (ether) – salivary and tracheobronchial secretion
   - To reduce secretions and also halothane induced ventricular arrhythmia (in vagal slowing down)
   - To prevent laryngospasm – increased respiratory secretions cause reflex laryngospasm
2. Peptic ulcer: Fasting and neurogenic phase only – Gastric phase not reduced – Not popular anymore
3. Pulmonary embolism: reduces reflex pulmonary secretions

Atropine: Therapeutic uses - antispasmodic

1. Intestinal and renal colic and abdominal cramps – not in biliary colic
2. Diarrhoea (nervous and drug induced) – Lomotil --- not in infective ones
3. Spastic constipation, IBS
4. Pylorospasm, gastric hypermotility, gastritis, nervous dyspepsia etc.
5. Urinary frequency and urgency and nocturnal enuresis (children) - ???
6. Dysmenorrhoea

Atropine: Therapeutic uses – Bronchial asthma, asthmatic bronchitis and COPD

- Reflex vagal activity – bronchoconstriction and increased secretion – in bronchitis and COPD – lesser in asthma
- Oral Atropine – bronchodilatation
  - Disadvantages: dry up secretions in RT – inspissations and plugging in bronchioles – collapse – plus decreased mucocilliary clearance
  - Inhaled Ipratropium Br – does not decrease secretions and impair mucociliary clearance - useful in bronchitis and COPD
  - For regular prophylaxis – not to terminate acute attack

Anticholinergics -Mydriatic and Cycloplegic - Ophthalmic uses

- Used as eye drop or ointment:
  - Diagnostic: Atropine 1% ointment is used
    - Measurement of refractive error – mydriasis and cycloplegia
    - Preferred ones: Homatropine, Tropicamide and cyclopentolate – shorter action
    - However – no cycloplegia in children by newer ones
    - Atropine 1% ointment still preferred in children below 5 yrs
  - Ophthalmic examination of retina – fundoscopy (shorter acting preferred)
  - Therapeutic :
    - For resting eye: Iritis, iridocyclitis, keratitis, corneal ulcer etc.
    - Alternating with miotics (prevention of synechia)

USES OF ANTICHOLINERGICS – CONTD.

- **CVS:** Myocardial Infarction, Digitalis toxicity – to counteract reflex vagal bradycardia and partial heart block
- **Parkinsonism:** Mild cases of parkinsonism (early cases), Drug induced Parkinsonism and adjunct to Levodopa
- **Motion sickness:**
  - Hyoscine (scopolamine) is the drug used – Oral, injection and transdermal patch
  - 0.2 mg orally given as prophylaxis before journey – lasts 4-6 hours – transdermal preparations
  - Not effective in other type of vomiting
- ***Twilight sleep*** and ***maniacal states: Hyoscine -*** sedation and amnesia – lie detector
- Atropine: Antidote for Anti-ChE & Mushroom poisoning, and to block Muscarinic effects of Neostigmine, Cobra envenomation

ANTICHOLINERGIC - ADRS

- Commonly occurring but of non serious type
- Mydriasis and cycloplegia – using as antisecretory or Preanaesthetic medication
- Belladona Poisoning: Drug overdose and consumption of seeds of berries of belladona/datura
  - Symptoms:
    - Dry mouth, difficulty in swallowing and talking
    - Dry, flushed and hot skin (face & neck), fever, decreased bowel sound, dilated pupil, photophobia, difficulty in micturation
    - Excitement, psychotic behavior, delirium and hallucinations
    - Hypotension, weak and rapid pulse, respiratory depression and cardiovascular collapse
    - Convulsions and coma

Belladona Poisoning - Treatment

- **Diagnosis:** Methacholine 5 mg or Neostigmine 1 mg SC – no muscarinic effects
- **Treatment:**
  - Gastric lavage in case of ingestion – tannic acid
  - Dark Room and cold sponging and ice bags
  - Physostigmine 1–3 mg SC or IV
  - Maintenance of blood volume, assisted respiration and Diazepam to control convulsions
  - Other supportive measures

ANTICHOLINERGIC - CONTRAINDICATIONS

- **Glaucoma** – Narrow angle (Precipitation of angle closure)
- **BHP** – urinary retention
- **Acid peptic ulcer diseases** (Non-selective ones) – precipitation of symptoms

Drugs acting on Ganglions

Drugs acting on Autonomic ganglia

- ACh is excitatory neurotransmitter - parasympathetic and sympathetic
- Drugs which inhibit synthesis or release – interfere with ganglionic transmission
- N_N mediate rapid depolarization of ganglion cells
  - also present are M_1 & M_2, adrenergic, dopaminergic, amino acid, peptidergic receptors - slow – mediate slowly developing and longer lasting effects
  - Released from preganglionic cholinergic terminals – but by themselves
  - One transmitter – one cell junction ... Over simplification

Ganglion stimulants and blockers

- **Ganglion stimulants:**
  - **Selective agonists:** Nicotine (small dose), Lobeline, DMPP, TMA and Varenicline
  - **Non-selective:** Acetylcholine, carbachol, Pilocarpine, Anticholinesterases
- **Ganglion Blockers:**
  - Competitive blockers:
    - **Quaternary compounds:** Hexamethonium, Pentolinium
    - **Secondary/tertiary:** Mecamylamine, Pempidine
    - Monosulfonium compound: Trimethaphancamforsulfonate
  - Persistent depolarizers: Nicotine (large dose) and Anticholinesterases (large doses)

NICOTINE

- Source – alkaloid in *Nicotiana tabacum*
- Action – stimulation of Para symp and symp ganglia via N_N and N_M receptors at low dose
  - Large doses – persistent depolarization
- **Only Indication** – short term nicotine replacement in tobacco abstinent Subjects

PHARMACOTHERAPY OF SMOKING CESSATION

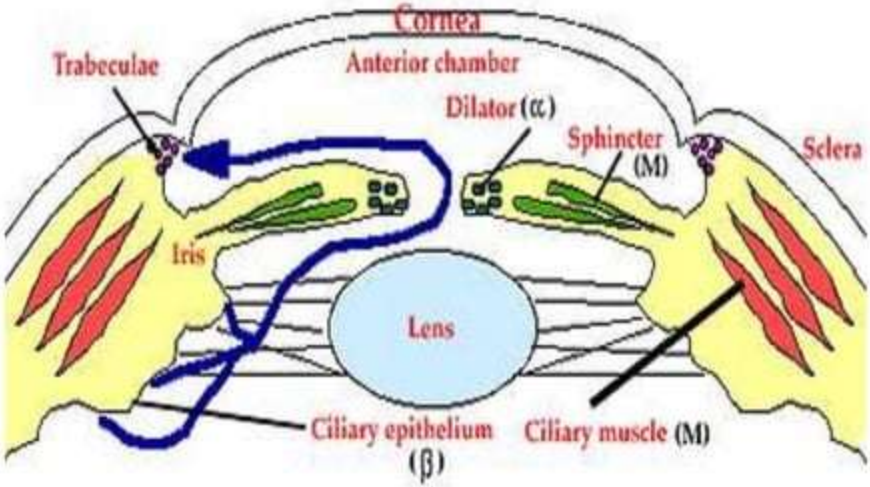
- Difficult to quit - Nicotine dependence – counseling and motivation
- Aim of treatment:
  - To reduce the craving for satisfying (reward) effects of nicotine
  - To suppress the physical withdrawal symptoms
- Drugs: Nicotine replacement, Partial agonists of α4β2 Nicotinic receptors (Varenicline) and antidepressants (Bupropion)
- Nicotine transdermal: once daily on the hip/abdomen/chest/upper arm – supresses nicotine withdrawal but craving only partially (10, 20, 30 cm2 patches)
  - Also nicotine chewing gum - alternative of patches (NULIFE 1, 2, 4 mg chewing gums)
  - ADRs of nicotine replacement: headache, dyspepsia, abdominal cramps, loose motion, flu like symptoms etc

VARENICLINE

- Partial agonists of α4β2 NR receptor
- MOA: Reinforcing effects mediated by α4β2 NR – nucleus accumbens and mesolimbic areas
  - Normally, activation of α4β2 NR by nicotine – induces DA release – satisfaction/reward and reinforcing effect
  - PA activity of varenicline - nicotine substitution, but blocks reward effects of smoking
  - Reduce craving and withdrawal symptoms
  - Comparable to nicotine replacement and Bupropion
- ADRs: Mood changes, irrational behaviour, appetite and taste disturbances, sleep disorder and agitation – suicidal thoughts
- Bupropion: atypical antidepressant – discussed elsewhere
- Ganglion blockers – no clinical use anymore

Summary

- Atropine and its Pharmacological Effects
  - Therapeutic uses of Atropine
  - Mechanism of Mydriasis and Cycloplegia
- Names of Atropine Substitutes with their Uses
  - Details of Atropine Substitutes – Ipratropium bromide, Dicyclomine, Oxybutynin
- Treatment of Atropine Poisoning
- Names of Ganglion Stimulants and Blockers Drugs – antismoking drugs (short note)


Cornea
Trabeculae
Anterior chamber
Dilator (α)
Sphincter (M)
Sclera
Iris
Lens
Ciliary epithelium (β)
Ciliary muscle (M)

THANK YOU