

Parasympathomimetic (Cholinomimetic drugs)

G3FR_8

		Direct				Indirect					
		Choline esters			Cholinomimetic Alkaloids	Reversible			Irreversible		
Drug		Ach	methacholine	Carbachol	Bethanechol	pilocarpine	physostigmine	Neostigmine	Neostigmine substitutes	Organophosphorus Compounds	
P/K	Abs	Poorly absorbed &				Well abs orally	Complete oral abs	Partial oral abs	Neostigmine substitutes	all sites even intact skin except Echothiophat	
	Dis	"hydrophilic" Poorly distributed to CNS				BBB		Not pass BBB			High lipid soluble & BBB
	Met	True & pseudo	True only	Not metabolized by cholinesterase			cholinesterase				1- Edrophonium
	T1/2	Very short	longer		More long		short				Long "till synthesis of new enzyme"
MOA		Bind to and activate muscarinic and/or nicotinic receptors				Bind reversibly with anionic & esteratic site of cholinesterase → ↑ Ach			Bind reversibly with anionic site of cholinesterase → ↑ Ach	Phosphorylate Ch.E esteratic site "1st reversible then irreversible aging" → ↑ Ach	
Muscarinic		+++		++		++++		Selective on skeletal muscle	+++		
Nicotinic		+++	None	+++	None	+++ & CNS	+++ & (No CNS)		+++ & CNS		
selectivity		No selectivity	Heart	Eye, GIT, Urinary	GIT, Urinary	Eye, secretion	Eye, CNS		GIT, U.B, SK.M (Direct & indirect)	They are:	
Muscarinic action									USES	1- Thiophosphate insecticides:	
Eye (M ₃)		- (+) constrictor pupillae muscle → resulting in miosis. - (+) ciliary muscle → accommodation to near vision - ↓ I.O.P due to opening of filtration angle and canal of schlemme - ↑ lacrimation - lid twitches (<i>Nicotinic</i>)								1-Diagnose myasthenia gravis 2- ttt of myasthenia crisis 3- Differentiation between: myasthenia Crisis → improves cholinergic crisis → worsen	- Parathion - Malathion (malathion metabolized into inactive products in birds & mammals but not in insects or fish)
CVS		- Heart → ↓ all cardiac proprieties → hypotension (M ₂) - Blood Vessels → V.D (Via EDRF or NO cGMP) → hypotension (M ₃) End result of muscarinic effect → hypotension								2- Pyridostigmine Ambenonium	2- War gases - soman - sarin
Respiratory		-bronchospasm, ↑ bronchial secretion (M ₃)									3-Eye drops
Exocrine Glands		↑ all secretion of glands [sweat, Lacrimal, salivary, gastric, pancreatic] (M ₃)									- Isoflurophate - Echothiophate
GIT, Urinary		- (+) wall (M ₃) & Relax sphincter (M ₂) - ↑ secretion (saliva, HCL)									Organophosphorus poisoning
Nicotinic action											
Nm (MEP)		Skeletal muscle twitches e.g. the eye lid twitches muscles.						Indirect Muscle twitches	Direct & indirect Muscle twitches	- longer duration than neostigmine & more specific - Selective on Sk.M -used in myasthenia gravis	Cause: inhalation, suicidal & wars. Manifestations: Muscarinic: -Abdominal pain -diarrhea, -bronchospasm-bradycardia -sweating -salivation Nicotinic: Muscle fasciculation → paralysis. CNS: Confusion, convulsions then CNS depression. Cause of death: Respiratory failure
Nn		(+) Parasympathetic ganglia → ↑ Ach → hypotension (+) sympathetic ganglia → ↑ N.A → hypertension (+) Adrenal medulla → ↑ adrenalin → hypertension End result of nicotinic effect hypertension						CNS action			
N.B		A.ch in small dose → hypotension A.ch in large dose after atropine → hypertension due to (+) adrenal medulla & autonomic ganglia "N action" → ↑ catecholamine (A.ch reversal)								3- Benzpyrinium used in: - paralytic ileus - urine retention	
Uses		1- Experimental use		-Postoperative paralytic ileus -Postoperative urine retention		1- Glaucoma. 2- Counteracts mydriasis after fundus examination. 3-To cut recent adhesion between iris and lens [alternatively with mydriatics]		1- Glaucoma "Eye drop" 2- paralytic ileus 3- urine retention 4- Myasthenia gravis 5- atropine toxicity "Antidote" 6- Curare poisoning "Antidote"		4- Demecarium Specific for Glaucoma	Management 1-Removal contaminated clothes, wash skin by NaHCO ₃ . 2-Gastric lavage. 3- Aspiration & Artificial respiration 4- Atropine (lifesaving): • It blocks peripheral & CNS manifestations. • 1mg I.V /10 min till full atropinization (Mydriasis, Dry mouth, Tachycardia) • The patient is kept atropinized for 24 h 5- Cholinesterase reactivators (oximes): •PAM (pralidoxime) •DAM (diacetylmonoxime): better pass BBB - Reactivate recently inhibited enzymes. - They break bond between enzyme & organophosphate. - Useful in early cases before aging -protect enzymes from further inhibition. 6- Anticonvulsant: e.g. diazepam.
Muscarinic Side effect		-Abdominal cramps -Bronchospasm -Sweating -Diarrhea -Flushing -Hypotension +((convulsion coma death(↓R.C)"physostigmine")) -Bradycardia -Salivation -Headach									
Nicotinic S.E		Muscle Twitches									
C.I.		1-Brochial asthma (bronchospasm). 3- Hyperthyroidism [AF can occur] 5- Hypotension (case vasodilation)		2- Angina pectoris [↓ blood flow so, decrease coronary flow]. 4- Peptic ulcer (++ Gastric secretion)				Treatment or toxicity 1-Stomach wash 2- Oxygen and artificial respiration 3- atropine 4- Anticonvulsant in case of seizure			
Myasthenia gravis						Alzheimer disease					
Definition		Autoimmune disease characterized by Abs against A.ch at MEP				A/E: a) deficiency of cholinergic transmission in basal forebrain. b) over-excitation (NMDA) glutamate receptors					
Diagnosis		Edrophonium IV or neostigmine SC + Atropine (block muscarinic action) → improvement.									
Treatment		1-neostigmine or Pyridostigmine + Atropine. 2- ephedrine or caffeine (adjuvant potentiate neostigmine & facilitate NM transmission) 3- Steroids (prednisolone) or immunosuppressant (azathioprine Thymectomy, Plasmaphoresis to wash antibodies)				Treatment (1) Cholinesterase inhibitors(central): ttt of mild & moderate cases. A) Tacrine: hepatotoxic. B) Galantamine, Donepezil & Rivastigmine: more selective & safer. (2) NMDA-receptor antagonist: Memantine (in severe cases)					
Drugs CI in MG		Skeletal muscle relaxant, Aminoglycosides & β-blockers									
		Cholinergic crisis		Myasthenia crisis							
Definition		severe muscle weakness due to over treatment with anticholinesterase drugs [sustained depolarization]		severe muscle weakness due to under treatment with anticholinesterase Drugs							
Edrophonium →		more weakness		muscle improvement.							

Parasympatholytics “Muscarinic Antagonists or Anti-muscarinic drugs”

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Natural alkaloids	Atropine						Hyoscine	
P/K	- Well absorbed from all sites except intact skin “Tertiary amine” - Passes BBB -Metabolized in liver - Excreted in urine, enhanced by acidification of urine						Shorter duration	
Actions	Antimuscarinic actions					CNS actions		
	C.V.S	Eye	GIT	Exocrine glands	Urinary tract	Respiratory	Mainly stimulant	
	<p>Heart: tachycardia mainly in young people: (as vagal tone at rest is the highest), often absent in elderly</p> <p>- I.V. injection → paradoxical bradycardia followed by tachycardia due to:</p> <p>- (+) C.I.C</p> <p>- (-) presynaptic M₂ receptor → ↑ A.Ch</p> <p>Blood vessels:</p> <p>- Therapeutic dose → no effect</p> <p>- L.D in children → V.D “atropine flush”</p> <p>Blood pressure:</p> <p>- Therapeutic dose → no effect</p> <p>- Reverse hypotension of A.ch, carbachol & neostigmine “N&M”</p> <p>- Abolish hypotension of Methacholine, Bethanechol & Pilocarpine. ”M”</p>	<p>-Passive mydriasis (paralysis of C. P.M.)</p> <p>- Cycloplegia (paralysis of ciliary muscle) → near vision is impaired</p> <p>- ↑ I.O.P</p> <p>- ↓ lacrimation</p>	<p>-Relax wall “antispasmodic” & contract sphincters</p> <p>- inhibit secretion → constipation.</p>	<p>Decrease all secretion except milk, bile & urine</p> <p>- dry eye → ↓ lacrimation</p> <p>-Dry mouth → ↓ salivation</p> <p>-dry skin → ↓ sweating → flush</p> <p>-slightly ↓ HCL</p>	<p>- Relax wall & contract sphincters → urine retention</p> <p>- Relax ureter</p>	<p>-Bronchodilatation</p> <p>Not used in B.A due to:</p> <p>- Dry, viscid & thick bronchial secretions (difficult to be expelled).</p> <p>- ↓ Mucociliary clearance in bronchi → accumulate secretion</p>	<p>Stimulant</p> <p>- ↑ R.C.</p> <p>- ↑ C.I.C</p> <p>- Mild Restlessness, higher doses → agitation, hallucination, mania, convulsion → depression</p>	<p>Mainly depressant</p> <p>- ↑ RC</p> <p>- Hallucinations in over dose</p>
							Depressant	
						<p>- ↓ Vomiting center.</p> <p>- ↓ parkinsonism</p>	<p>- Anti-motion sickness</p> <p>- Sedation & amnesia</p>	
USES	- Pre-anesthetic medication							
	<p>- ↑ R.C → # depressant effect of anesthetics.</p> <p>-secretions → # aspiration pneumonia</p> <p>- Bronchodilatation</p> <p>- protect heart from vagal tone & bradycardia induced by general anesthetics</p>						<p><i>Better than atropine</i> due to</p> <p>- less tachycardia “safe in thyrotoxic patient”</p> <p>- More CNS depression</p> <p>- (++) R.C</p> <p>-Strong anti-secretory</p> <p>-Strong anti-emetic</p>	
	- Antidote in organophosphorus poisoning “life-saving”							
	- Heart block as in: digitalis toxicity Infarction verapamil or BBs	-Mydriatic in children during: -fundus examination -measurement of refractive errors -iridocyclitis to cut adhesions.	- colic -Peptic ulcer. -Anti-emetic		- Urinary incontinence	- Bronchial asthma (Ipratropium better)	- Parkinsonism	
Side effect Atropine Toxicity	Tachycardia	-Blurring of vision acute glaucoma (↑ IOP). -Mydriasis	constipation	-Dry mouth -Atropine flush (hot, red, dry skin) - fever esp in children	Urine retention (especially BPH)		Agitation, delirium Convulsion then coma & (-) R.C “Cause of death”	
CI	Angina & Arrhythmia	Narrow angle glaucoma	Constipation, paralytic ileus		BPH			
ttt of toxicity	1-neostigmine “antidote” -- (physostigmine “block central & peripheral symptom” but dangerous) 2-Gasteric lavage with tannic acid 3- Sedative as diazepam 4- cold fomentation 5- Artificial respiration with O ₂							
Synthetic atropine substitutes	Mydriatics			Anti-secretory Anti-spasmodic		Urinary incontinence	Anti-asthmatic	Anti-parkinsonism
		Atropine	Homatropine	Tropicamide,Cyclopentolate	-Atropine methyl nitrate	-Oxybutynin	- Ipratropium	- Benzotropine
	Duration	7-10 days	24 h	6h	relax pylorus in Hypertrophic Pyloric Stenosis	-Emepronium	- Tiotropium	- Benzhexol
	Cycloplegia	+++	++	+	-Hyoscine N-butyl bromide, - Propantheline - oxyphenonium	-Tolterodine (# M ₃)		
	Uses	measurement of refractive errors iritis			relax spasm of GIT and urinary tract -Pirenzepine, telenzepine (# M ₁): ttt of peptic ulcer			
Drugs have atropine like action	1-Anti-depressant “tricyclic”. 2-Anti-histamines “1 st generation”. 3-Anti-arrhythmics “quinidine & disopyramide” 4-Anti-psychotics “typical group” 5-Analgsics “pethidine” 6-Atropine substitutes							

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