ACETYLCHOLINE (Direct-Acting)

Quaternary ammo. compound, can't pero. membs. → H_2O soluble and rapidly Hydrolysed, so No therap use

Multiplicity of Action

Rapid inactiv. by AchE

Both Musc. & Nicotinic Action. (Pre-gan, and post ganglan of Parasymp

ACTIONS

Heart — (M2) [Frechronotropic effect]

- ↓HR → -ve chronotro
- ↓Force → -ve inotropic
- ↓ conduction velocity → -ve dromotropic

due to ↓ firing at SA node & AV node (BY Hyperpolarization of b.V

- mimic vagal (parasym.) stimu.
- ↓ HR • ↓ SV (stroke vol.)
- ↓ B.P by indirect mechan

(Ach activate M3 on endothelial smooth muse → diffuse to smooth muscle cells → NO produce from arginine → ↑ protein Kinase G product → Hyperpo. → Smooth muse. Relaxa via Phosphodiesterase-3 inhibig (vasodilation)

[PDE-5-Inhib = pulmonary HT treatment : Sildenafil).

Other Actions

- salivary secretion
- lacrimation
- Intestinal secre. • motility ↑ tone
- Bronchiolar secre.
- urination → Detrusor contract → Trigone & Sphinct → Relax
- Stimulate ciliary muscle/circular Contrac. for near vision
- Miosis (ACh 1%).

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atropine

PHYSOSTIGMINE

A.K.a Eserine due to eserine nucleus

(Indirect-Anti-AchE) (Reversib)

- Nitrogenous Carbamic acid ester
- Tertiary amine (Lipid solub) • substrate for AchE
- form stable carbamoylated interme E enzym (reversible)

-ACTION

- Stimulate muscari, Nicotin sites of PANS as well as nicotin recep of NMJ
- Durati = 30min – 2hr (Interm. acting)
- enter & Stimulate CNS

-Therapeutic uses

- ↑ se intestinal & bladder motility So use in atony of any of these organs
- DOC antidote of 1) atropine [CNS effect of atropine 2) Cardiac effect of TCAs]

- ADR
- convulsions (high doses on)
- Bradycardia
- Inhibit AchE at NMJ → Ach accumulate → paralysis of Sket. muscle (NOT occur on therap. Dose)

→ Pralido. can't reverse its effect

⊖NM-block GIT

NEOSTIGMINE

(Indirect-Anti-AchE) (Reversib)

- Carbamic acid ester
- inhibit AchE similar to physo.

- ACTION

Q.A = H_2O solub

- has quaternary N → Polar mole – poorly absorbed
- NOT enter CNS
- effect at skeletal musc. greater than physosti. (contrac. → paralysis)
- Duration 30min – 2hr.

- Appli

- Stimulate bladder & GIT
- Antidote (imp) for competitiv NM-bloc. agent
- manage symp of myasthenia gravis (DOC) (chronic autoimm NM disease = muscle weak → breathing muscle, movement muscle leg & arm).

- ADRs:

- gener. cholin. stim.
  - Salivation
  - Flushing
  - ↓ B.P
  - N/D
  - Abd. pain
  - NO CNS effect

CI → intest or urinary obstruction

- parathion & malathion (irrev. anti AchE) used as insecticides.
- pralidoxime → reactivate AchE (2-PAM)
  - ↳ unable to penetrate CNS
  - ↳ Ib given befor aging of alkyl. enzy → reverse musc. & nicotinic peripheral effect of organo BUT NOT CNS eff
  - ↳ also itself a weak AchE inhibitor (esp at high doses)

Aging = loss of alkyl gp.

Bethanechol (Direct-Act)

- unsubs. carbamoyl ester
- NOT hydrolys. by AchE
- Lack NICOTINIC, STRONG Muscari. ACTION
- Major action smooth mus. of bladder
- DOA = 1 hour.

ACTION: ↑ intestin. motility & TONE
Urination → stimulate detrusor
→ Relax Trigone & sphincter

- Applic. (bladder never damaged)
- Stimulate atonic bladder
- Neurogenic atony
- Non-obs. urinary retention
- megacolon (dilatation of colon)
- ADRs: sweating, saliva., flushing, ↓BP
  N/D bronchosp.

PILOCARPINE: (Direct actin)

- Tertiary amine
- less potent
- uncharged. penetrate CNS
- exhibit muscarinic activ.
- primarily in opth.
- ACTION:- Non-speci
- Appl. TOPICALLY
- Rapid miosis & contrac. of ciliary musc., the vision fixed at some partic. distance [Focus]
- potent stimulator of secreti
- Treat xerostomia (sjogren syndrom. treated ē oral pilocarp. tab. & cevimeline) (dry mouth, lack of tears)
- Applic.: Glaucoma (open & angle-closure)
  [open Trabecular mesh → ↓↓ IOP in few minutes duration 4-8 hrs] esp. in EMERGENCY SITUATION
- ADR:- Blurred vision, Night blind.
- Brow ache

TOXICITY → excess salivation & sweating similar to mushroom poisoning [genus Inocybe]: antidote is parenteral atropine
Antidote for mushroom = Thiotic Acid

EDROPHONIUM: (Indirect-reversible Anti-cholinest.)

- Diagnosis of myasthenia gravis
- Anti-dote for competiti NM-blocker.
- short duration of action (10-20min)
- PROTOTYPE of AchE inhi (among NEO, PYRI)
- Rapid abs. - Quaten Amine
- Limited use. H_2O-solub.
- Action limited to periphery.
- Injection = Rapid Asr in muscle strength

Carbachol (carbamylcholine) DT

- BOTH MUSCARIN & NICOTINIC
- Like bethan., ester of Carbanic Acid

ACTION: ON CVS and GIT, first stimulate, then depress

- cause release of epi from adren. med. by nicotin. action [Non-selective]
- Miosis (TOPical.)

Applic (Rare) uses except as Miotic agent, treat glaucoma [↓IOP, pupillary contracti

ADRs: At opth. dose → little/lack of S.E due to lack of sys. penetration
(quater. amine) C = carbachol, C = common (N, M)

ECHOTHIOPHATE:- Indirect Acting

(ANTI-CHOLINESTERASE, Irreversible)
(ORGANOPHOSPHATE)

Echo + AchE → permanent inactivation
(POH) (OH) enzyme (alkyl gp) slowly release
from AchE → aging → make it imp. for pralidoxime to break the bond.

ACTION:

- generalized cholin. stimulc
- paralysis of motor function (breathing diffi
- convulsions
- intense MIOSIS
- outflow of aque. humor → ↓IOP

- Therap. Applic:
- open-angle glaucoma
- rarely use due to risk of (cataract)
- long duration of act. (100 hours)
  Antidote for toxicity: high dose of Atropine.

RIVASTIGMINE, GALANTAMINE

- DONEPEZIL [Donepezil = mostly] Reversible inhibitors of AchE
- First-line treat for Alzheimer's disease, Though confer modest benefit
- ↓ Healthcare cost (Anti Alzheimer drug)
- can be used ē memantine (N-methyl-D-aspartate antago. ē Glutamate & Glycine binds to it normally = Excitatory
  moder. to severe disease
- Hepatotox
- (GI distress ADR) ★ Tacrine = replaced

NON-Depolarizing NM-blo

- Block cholinergic transmision b/w motor nerve ending & nicotinic recep. on skeletal Muscle
- They act as Antagonist
- First drug was curare
- They have ↑se the Safety of anesthesia

Mechanism

At Low doses

Competitively block Ach at nicotinic recep.

- Effect can be reverse by adm. cholinesterease inhibitors → ↑se Ach

At high doses

Block ion channel of motor endplate

↓

↓se ability of cholinesterase inhibitor to reverse the action of Non-depol. blockers.

ACTION:

Small contracting muscles of face & eyes > fingers > limbs > Neck > trunk muscle > intercostal muscle > Diaphgram

[order of contracting muscle blockade]
[recover in reverse manner]

KINECTICS:

- minimal oral abs.
- Given IV or IM (rarely)

[2 or more quaternary amine in their bulky ring struc → ↓se absorp.

- Don't cross BBB

APPLI = Adjunct in anesthesia

D.I = (1) cholinesterase inhib
(2) Halogenated HC anesthetic (Desflurane → sensitize NMJ)
(3) Aminoglycoside Antibiotic = inhibit Ach release by competing ē Ca^{2+} ion = ↑se blockade.
(4) Ca^{2+} channel blocker.

ADRs

↓ B.P. ↑ H.R (vagolytic) • Post-oper muscle pain
• ↑se IOP & intragastric pres
• ↑ K^+ • ↑ Histamin • Malignant Hyperthermia

- Atracurium & cis-Atra- meta. via Hofman rex & don't req. enzymes.

Depolarizing NM-Blockers

- Blocks cholin. transm b/w moter nerve ending & Nicotinic receptors Skeletal Muscle
- Act as agonist on endplate NMJ
- work by depolarizing the memb.
- Similar to Achr, & resistant to AchE
- Succinylcholine — only Dep. NMB.

Mechanism

PHASE - I

open Na^+ channel assoc. ē Nicotinic recep → depolarization → Transient Twitching

PHASE - II

(Fasciculation) muscle soreness

continued binding → render receptor incapable of transmitting impulses

↓

with time, continue depolar → gradual repolari → Na^+ channel close

↓

Resistance to depo. & FLACCID PARALYSIS

ACTION:-

- duration: short due to rapid hydrolysis BY PSEUDO-cholines.
- At NMJ — NOT metabs by AchE
- Fasciculation that causes muscle soreness is prevented by adm of small dose of Non-depo. prior to SC

APPLICATION — ET - EC

- useful when endo-tracheal intubation is req during induction anesthesia
- Electroconvulsive shock treatment

KINECTICS IV — iv infusion to main.

longer duration — due to pseudocho.

ADRs:

- Hypertheimia • Hyperkalemia
- Aprea [in pts ē ↓ cholinesterase ⇒ rapid release of K^+]
  ⇒ caution / Avoid co-adm ē Digoxin / Diuretic / HF patient

apnea: breathing stops & restarts many times when u sleep

CHOLINERGIC ANTAGONIST

ATROPINE [PROTOTYPE]

L-Atropin = More Active

- Tertiary amine
  - Competitive inhibitor
  - Rapid absorb
  - meta by liver
  - exc. - urine
- belladonna alkaloid
  - Atropa belladona
  - Basic Nature
  - Duration = 4hr
  - Topical app = duration "days"
  - half-life = 4hrs
- HIGH AFFINITY FOR muscarinic receptors
  - Act both centrally & peripherally
  - greatest inhibi effect on bronchial tissue & secretion of sweat & saliva.

Constriction = Active
Relaxa = Passive

ACTIONS - Back.

of both circul/radial (visceral) (cardiac Exocrine

EYES - relax iris-sphinc (circular)

Passive (5mg)
- Mydriasis (dilation)
- unresponsive to light
- cycloplegia (inability to focus for near vision)
- ↑ses IOP

GI

Atropine as active isomer, L-Hyoscyamine
- Anti-spasmodic
- HCl production NOT significantly affected

doses of atropine that ↓ spasm also ↓se saliva secret, ocular accomodation & urination → ↓compliance

Cardiovasc.

- 0.5mg: low doses → Slight ↓se in HR (due to M1 blockade on inhibitory pre-synap neuron → ↑Ach release)
- 5mg: high dose → ↑se HR by M2 blockade on SA node

Secretions

0.5mg-5
- dry mouth
- sweat & lacrimal gland also affected

↓ sweat = ↑se body Temp

Ach ↑se = SLUD
Atropin ↓se = SLUD
Secretion | urine
lacrimal
Defeca-tion

Paralysis of accomodation

THERAPEUTIC USES

Opthalmic
- Mydriatic } ↓ our intraocular & accomodative capacity of eye
- cycloplegic }
- Measurement of refractive errors
- Short-acting Antimusc. (cyclopentolate & Tropicamide replace ATROPINE) 7-14 day v/s (6-24hr) DoA
- α-adreng. drugs (PE) preffered for dilation if cyclople. Not req.

Anti-spas
Relax GIT

CV
Treat Bradycar.

Anti-secre
- Block secret. of resp. tract, use before surgery

Antidote
- organophosphate (insecti & nerve gases)
- physostigmine
- Mushroom
- CNS toxicity of anti-cholinesterases

ADRs

Brain (+) PM1 = [cognitive function]

- Dry mouth
- Blurred vision
- Sandy eyes
- Tachycardia
- Urin. retention
- constip
- confusion
- Hallucin.
- Depress
- Restlessness

>10mg dose

- circulat & resp. collapse

Dose-dep. effect

0.5mg	2mg	5mg	>10.0mg
↓HR, Dymouth, ↓sweat	↑HR, Dry mouth, Blurred vision	↓HR, papitation, Dilation of pupil	Hallucination, Delirium, Coma

SCOPOLAMINE
Buscopan · Hyoscine butylbromide
a.k.a Hyoscine

- Tertiary amine · CNS as well as periphe
- long duration, comp. to atropine

Actions
- unusual effect of blocking memory
- sedation at high doses
- excitement, euphoria, abusive potential

Therapeutic uses:
- motion sickness · post-oper. Nausea vomitting
  - Topical patch (dur. = 3 days)
  - most imp prophylactically

Kinetics similar to Atropine

IPRATROPIUM Br & TIOTROPIUM Br
- Both're quaternary amine, derivatives of atropine
  - COPD → for bronchodilation.
- BOTH given via inhalation
- Ipratro → Asthma (dilation)
- BOTH 've +ve charge & don't enter systemic or CNS circulation
- Tiotrop — given once daily (adv. over ipratro) ↓ QID

Tio = QD
Ipra = QID

Benzhexopine & Trihexyphenidyl
Atropin Derivs
- adjunct ē Anti-parkinson's and other similar symp, including anti-psychotic, EPS ₂ ₃ [In Parkinsonism ↓DOPA ↑ACh]

GANGLIONIC BLOCKERS
- Act NICOTINIC recep of both parasy and sym autonomic ganglia
- These agents have NO selectivity against Small dose = Agonist Normal for para and SYP

NICOTINE: - Large dose = Persistent Depolarization

- component of cigratte smook
- Dep. on dose → depolarize autonomic ganglia (Otherwise ↑BP ↑HR)

Result in first in ↵
Stimulation → Then paralysis of ↑ all ganglia [At high doses = ↓B.P ↓GI, bladder activity]

Stimulatory effects are complex & result from ↑ses release of Neurotransmitter (NT)

Nicotine – [↓Tension ↑Attension/Arousal ↑mood (pleasure) ↓Apprehension]

Dopamine	NE	Ach	Glutamate	Serotonin
• Pleasure • appetite suppression	↓ • Arousal • Appetite supp.	• Arousal • cognitive enhanc.	↓ • learning • memory enhancement	• mood modul. • appetite suppre.

↓
β-Endorphin
• reduce Anxiety & tension

GABA
• ↓ anxiety & Tension

Tropicamide & Cyclophenolate
Atropine Derivatives
- use as opthalmic soln
  - Mydriasis
  - cycloplegia

Duration
- Tropica 6hrs
- Cyclop 24hr.

Daifenacin, Fesoterodine, Oxybutynin, Solifenacin, Tolterodine & Trospium Cl
- Treat overactive bladder
- Block musc. recep → ↓se intravesical pressure → ↓frequency ← ↑se bladder capacity

S.E = Dry mouth, Consti, blurred vision

Oxybutynin = avail as TDS, less dry mouth, better tolerated

★ - Atropin. derivative - For Peptic ulcer
(Anti-choli) M1-blocker
- → Pirenzepine
- → Telenzepine (Back)

★ - Atro. derivative = Glycopyrrolate
For peripheral surgery Pre-anesthet

★ - Atro deriv = Anti-spasmo
- → Dicyclomine
- → Oxybutynin
- → Fluvoxate

DOF ≈ UFF (due to pain)