#10 PT.2
ANTI-CHOLINERGIC DRUGS
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Cholinergic Antagonist Drugs

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

-Anti-muscarinic drug (parasympatholytics.): Atropine-like drugs, Hyoscine (Scopolamine)
selective blocker for muscarinic receptors

-Anti-nicotinic drugs

1-Ganglion blockers: Used in experimental pharmacology. E.g. Nicotine, Trimethapan
-ganglionic blockade is rarely used therapeutically because The responses of the blockers are complex and mostly unpredictable.
-Show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia

2-Neuro-muscular blockers: Used in surgery to produce complete muscle relaxation
Nicotinic antagonists interfere with transmission of efferent impulses to skeletal muscles.
Anti-muscarinic anti-cholinergic drugs:
*Commonly known as anticholinergic drugs
*block muscarinic receptors, causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands.
*they do not block nicotinic receptors so have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia

**sources:**
- **Natural agents:** (Atropine, Hyoscine)
- **Semi-synthetic:** (Homatropine)
- **Synthetic:** (Ipratropium, Pirenzepine, Propantheline)

**Note:** Antihistamines, phenothiazides and some antidepressants (mostly tricyclic antidepressant) have anti-muscarinic effects

**Anti-muscarinic drugs:**
**Atropine (Hyoscyamine):**
*tertiary amine Alkaloids obtained from Atropa Belladona* with high affinity to muscarinic receptor it binds competitively and prevents Ach to bind
*Considered as prototype for parasympatolytics (anti-muscarinic drugs)*
**Hyoscine (Scopolamine):**

*Tertiary amine alkaid obtained from Hyocyamus niger plant (Datura Stramonium)*

*Peripheral effect same as atropine*

*Longer duration than atropine*

*Greater action on CNS*

**Clinical pharmacology of anti-muscarinic drugs:**

*Reversible (competitive) blockade of M receptors*

*Exocrine glands (secretion of sweat & saliva, bronchial tissue) are most sensitive*

*Gastric secretion is the least affected*

*Heart is intermediate*

**Note:** Atropine blocks all 3 subtypes receptors ($M_1$, $M_2$, $M_3$)

**Pharmacokinetics:**

**Absorption:**

*Natural and most tertiary amines: good*

*Tertiary amine =NH$_3$ have more affinity than secondary=NH$_2$*

*Wide distribution and cross BBB*

*Quaternary amines: poorly absorbed and poor crossing BBB because quaternary have a + charge (NH$_4^+$) so can’t cross the barrier which require lipid soluble substance (Ipratropium)*

*Atropine $t_\frac{1}{2}$: 2hrs means stay in the body for 4 hours except topically in eye for days*

*Partly metabolized in the liver and partly excreted unchanged in urine*
Pharmacodynamics:

**Exocrine glands: at low doses reduce secretions**
- Salivary
  * leads to dry mouth (xerostomia)
- Bronchial
- Sweet glands
  * raises the tmp of the body which is dangerous in kids and elders

-CNS:
* Central stimulant effects (Atropine because it can cross BBB)
* Some may produce sedation (Hyoscine (scopolamine) but at high doses produce excitement)
* Hyoscine (scopolamine) blocks M receptors in vomiting centre and has anti-emetic effect so it’s used as motion-sickness drug
* Toxic doses: hallucination, convulsion, coma

*Eye:
* Mydriasis (dilatation of pupil) & unresponsiveness to light
  - used when testing your eyes
* Cycloplegia (relaxation of the ciliary muscle) cause: blurred vision and impaired accommodation to near vision
  - inability to focus to near vision
* Decreased lacrimation (flow of tears)
  - leads to dryness in the eyes
* Increase IOP (intraocular pressure)
  - in patients with angle-closure glaucoma may dangerously increase
CVS:
**Depending in the doses**
*Central effect:*
Decrease heart rate (low dose)
*Peripheral effect:*
Blockade of vagus nerve and increase heart rate (higher dose)
ABP : (arterial blood pressure)
No change

Respiratory system:
*Bronchodilatation
*Reduced bronchial secretion
-sometimes used to stop secretion in upper and lower respiratory tract prior to surgery
*Ipratropium* (quaternary amine derivate of Atropine) inhalation:

Useful in asthma and chronic obstructive pulmonary disease (COPD), also in patient who are unable to take adrenergic agonists

GIT:
*Decrease salivation
  - dry mouth

*Decrease acid secretion
  - reduced HCl production

*Decrease motility

*Delay gastric emptying

*Prolong intestinal transit time
  - increases absorption

*Anti-diarrheal and anti-spasmodic effects
  - the fast contraction of GI leads to diarrhea so anti-cholinergic drugs relaxes GI and stops diarrhea
  - relaxes GI tract so used as antispasmodic drug
  - diarrhea can cause spasms

GUT:
*Relaxation of bladder wall

*Useful in inflammatory spasm and pains of the urinary tract

*Risky in patients with BPH (Benign Prostatic Hypertrophy)

Therapeutic uses:

1-CNS disorders:

*Parkinson’s disease
  * unknown etiology

*Drug-induced Parkinsonism as Phenothiazine (dopamine-blocker) (induced acute dystonias: sustained contraction of muscles leading to twisting, distorted postures)
  * because of dopamine blocker drugs

*Benztropine, Benzhexol: useful to treat Parkinson and other parkinsonian syndromes
*Motion sickness and vomiting and nausea: Hyoscine (scopolamine) oral, injection, trans-dermal patches

Ocular uses:

*In eye examination (Tropicamide) produce mydriasis and cycloplegia

*In iritis (Atropine eye drop) prevent synechia (adhesion of the iris to the lens)

Note:

- Atropine eye drops effects: 7 days

- Tropicamide eye drops effects: 4-12hrs

**Premedication: Hyoscine (scopolamine) and Atropine (use as adjunct in anaesthetic procedure)
- anaesthesia makes vasodialation so the distribution increases and the effect wont be long, Anti-muscarinic dugs makes vasoconstriction so the distribution reduces and the effect becomes longer

Bronchial asthma: Ipratropium inhalation. (produce bronchodilatation)

Cardiovascular:

Bradycardia and heart block following AMI (acute myocardial infarction):
Atropine

GI disorders:

*Anti-diarrheal

*Lomotil= atropine + diphenoxylate

*Anti-spasmodics (in intestinal colic, irritable bowel syndrome)
Atropine, hyoscine, clidinium, prifinium

Urinary disorders

*Urinary urgency with UTI (urinary tract infection)
*Renal colic

Cholinergic poisoning as:
- Irreversible CEI (choline esterase inhibitor) **insecticide poisoning**
- Chemical warfare intoxication.

*To counteract muscarinic effects
*(nicotinic effects cannot be reversed)*

*Atropine IV*
-the ability of atropine to cross BBB makes it a good antidote against anticholinesterase poisoning

**Adverse effects of anti-muscarinic agents:**
*Dry mouth*
- because of reduced salvation

*Blurred vision*

*Tachycardia*
- high doses increase heart rate

*Constipation*
- because of reduced GI motility and relaxation of GI

*Hot flushed dry skin & hyperthermia may occur with high doses*
- because of reduced sweating

**Contraindications:**
*Glaucoma*
- Increase IOP

*BPH (benign prostatic hyperplasia)*

Bladder wall relaxation and sphincter contraction-
Atropine poisoning:
*Hot flushed dry skin & hyperthermia
*Agitation, delirium, hallucination
*Convulsions & coma
*Treatment is symptomatic

Individual drugs:
Atropine
Hyoscine: -Buscopan
Clidinium: -Libraxam
Prifinium: -Riabal

Neuromuscular blockers (NMB):
-NMB drugs are minimally absorbed when given orally
-most drugs are excreted unchanged in urine
-vecoronium & recoronium & metabolites appear mainly in bile
1-Nondepolarizing (competitive) blockers

**The first drug known to block the skeletal NMJ was curare
*Neuromuscular blockers are clinically useful during surgery to facilitate tracheal intubation and provide complete muscle relaxation at lower anesthetic doses, allowing for more rapid recovery from anesthesia and reducing postoperative respiratory depression At high doses: Nondepolarizing agents can block the ion channels of the motor endplate. This leads to further weakening of neuromuscular transmission, thereby reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers. With complete blockade, the muscle does not respond to direct electrical stimulation.
*** Tracheal intubation, usually simply referred to as intubation, is the placement of a
flexible plastic tube into the trachea (windpipe) to maintain an open airway or to serve as a
conduit through which to administer certain drugs.

2- Depolarizing agents:
Depolarizing blocking agents work by depolarizing the plasma membrane of the
muscle fiber, similar to the action of ACh. Unlike ACh, which is instantly
destroyed by AChE, the depolarizing agent persists at high concentrations in
the synaptic cleft, remaining attached to the receptor for a relatively longer
time and providing constant stimulation of the receptor.

From the book:
** The depolarizing agent first causes the opening of the sodium channel
associated with the nicotinic receptors, which results in
Depolarization of the receptor (Phase I). This leads to a transient twitching of
the muscle (fasciculations). Continued binding of the depolarizing agent
renders the receptor incapable of transmitting further impulses. With time,
continuous depolarization gives way to gradual repolarization as the sodium
channel closes or is blocked. This causes a resistance to depolarization
(Phase II) and flaccid Paralysis.