pharmacology

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Zaman 3nkom :)
Doctor's slides are in BLACK and the explanation is in RED

PNS Pharmacology lecture 4

ANTIMUSCARINIC AGENTS

ANTIMUSCARINIC AGENTS long ago they were called parasympatholytic (stop the action of paraS system)
Also we can call them muscarinic antagonists.

They block M receptors thus antagonize ACH … so action will be the opposite of ACH action that we took in previous lectures (this lec. Is highly dependent on ACH actions ^^)

Atropine & Atropine Substitutes

Atropine

- It is a 3ry ammonium ester of tropic acid → well absorbed from **GIT** if given orally or from **conjunctiva** after ocular instillation & can **cross BBB**.(CNS action)

Mechanism of Action

- Atropine causes **reversible competitive blockade** of the actions of ACh at **muscarinic receptors** (nonselective for muscarinic receptors).

Pharmacological Actions

1. **CNS (sth new … we didn't talk that much about ACH action on CNS so we will not oppose its action here :(and just in this part I mean CNS actions dr said it is not that imp to know what M receptor that is blocked whether 1 or 2)**
   - Stimulates cardioinhibitory center (vagal nucleus) → initial bradycardia
   - Respiratory center stimulation (blocks M_2 receptors) as if M2 inhibit Res. center
   - Antiemetic (blocks M_1 receptors in vestibular pathway).
   - Antiparkinsonian (blocks M_1 receptors in basal ganglia).
   - Stimulation of vasomotor center
   - High doses → cortical excitation followed by depression

2. Eye (effects persist for > 72 hrs) (long duration)

- **Passive Mydriasis** (paralysis of constrictor pupillae).

(because dilator pupillae action unopposed now this is why we called it passive because we didn't stimulate d.pupillae) remember that d.pupillae is adrenergic and c.pupillae is muscarinic)

- **Cycloplegia** (ciliary muscle paralysis & loss of accommodation for near vision).

↓ Aquous out flow → ↑IOP → acute glaucoma (Dangerous in people at risk) mentioned in contraindications section ** in narrow anterior chamber

3. Secretions

#↓ Salivation (→ dry mouth), ↓ lacrimation (→ dry sandy eyes).feeling as if there is sand in your eyes)

 # ↓ Sweating (→↑ body temperature) remember that sweating decreases temp.) & ↓ bronchial secretions.

 # Gastric secretion is least affected. so, atropine is less efficacious than H2 blockers in reducing HCL)

4.Smooth Muscle

- GIT& Urinary: relaxes wall & contracts sphincters → constipation, urine retention & antispasmodic= anticolic (because it relaxes wall) which is a good thing to be used for
- Bronchi: Bronchodilation

5.CVS (remember ACH decrease all cardiac properties so here the opposite

- **Tachycardia (mainly)** & ↑AVN conduction (blocks M_2 receptors).

- **Initial bradycardia on IM/Sc injection**: initial central vagal stimulation(we just said that above in the CNS actions) & presynaptic M_2 block → ↑ ACh release.(focus here and remember that presynaptic m2 are inhibitory so when they are blocked… more ACH that will act on postsynaptic and cause bradycardia)

  (Initially there will be bradycardia and after a while there will be tachycardia and we said why)
- **Tachycardia+ VMC stimulation** → ↑ BP
- **Vasodilation** (histamine release). → ↓ BP

(main thing .. increased BP but in large doses we may have decreased BP)

###in CNS 1 morphine increase histamine release

In CNS 2 atropine increase histamine release (until now)

Clinical Uses Atropine

1. **Preanesthetic medication** → inhibits secretions - dilates bronchi - antiemetic - inhibits bradycardia - stimulates respiration.

2. **Hyperactive carotid sinus - heart block - bradycardia** (in infarction or digitalis toxicity).(in this pt .. the carotid sinus in the carotid artery is hyperactive and it sends impulses to the vagal nucleus to release ACH to cause bradycardia so we give atropine to cause tachycardia)
   Also in the case of heart block ..the same thing happen which is M stimulation and tachycardia)
3. **Antiemetic** in motion sickness

4. **Organophosphate poisoning**.(most imp things to do are suction of secretions and giving atropine)

5. **Cycloplegic in children** (atropine is preferred to atropine substitutes in children as their ciliary muscle is strong & atropine substitutes are weaker cycloplegics than atropine**).** **(**in adults atropine is not preferred because its action lasts for 72 hours !!!!) and loss of light reflex

6. **Travelers diarrhea** (+ **Diphenoxylate**) to ↑ constipating effect &↓ abuse.

Diphenoxylate is one of morphine compounds but have constipating effects so when we give it with atropine, the dose will be less than given alone, so less abuse)

Adverse effects of atropine & contraindications (CI)

All the adverse effects are from the actions so they are easy now ^^

1. Confusion, restlessness → hallucinations, delirium & mania
2. Dry mouth and skin
3. Hyperthermia (complete skin dryness)
4. Vasodilation & flushing
5. Tachycardia.
6. Blurred vision - photophobia
7. Acute glaucoma in patients with narrow anterior chamber **(CI: glaucoma)**.
8. Urine retention in old patients with enlarged prostate **(CI: enlargedprostate)**.
9. Constipation

Acute atropine toxicity: ** mnemonic :) **

1. Dry as bone	**2. Red as beet root**
3. Hot as hare	**4. Blind as bat**
5. Mad as wet hen	
6. Bladder loses its tone	**7. Heart runs alone**

We talked about it so nothing is new here too ^^

Peripheral actions:

1) ↓ Sweat → ↑ temperature → **Dry (decreased sweat) & Hot skin(increased temp)**

2) V.D. (increased histamine)→ **Flushed skin**

4) Eye: **Dilated & Fixed** Pupil(negative light reflex), **blurring** of vision and **diplopia**.

5) Constipation & Urine retention

6) ↑ Pulse, ↑ B.P. & ↑ Resp.

CNS:

Cortical excitation (restlessness, convulsions, hallucinations and delirium)

followed by depression (respiratory depression and coma)

Treatment of atropine poisoning

1- Symptomatic: VERY IMPORTANT

- **Cold foment**→ for atropine fever
- **Catheter**→ for urine retention
- **Sedative & tranquillizers** e.g. diazepam → in stimulation stage
- **Stimulants** e.g. caffeine → in depression stage

(because we said CNS there is stimulation followed by depression so according to which stage pt presents in we manage it differently)

2- Gastric lavage to decrease drug absorption because we are dealing with TOXICITY

3- Dialysis →↑ excretion

4-Physiological Antidote IMP

A-**P**ilocarpine (**p**eripheral action only)

B-**P**hysostigmine→ peripheral action + cross BBB → central action. (preffered)

Remember that antidote for phyostigmine is atropine :)

Atropine Substitutes

I. Natural atropine substitutes

Scopolamine (Hyoscine)

	Atropine	Scopolamine (Hyoscine)
CNS effect	**Excitatory** **(it is stimulatory but in cases of toxicity it is followed by depression)**	**Depressants** → amnesia, fatigue, drowsiness, twilight sleep High dose → excitation
Antimuscrinic effect	More on **heart, bronchi and intestine**	More on **eye and secretions**
Antimotion sickness	++	+++
Duration	**Longer**	**Shorter**

Uses

- **Mydriatic** (briefer than atropine).
- **Antiemetic** in motion sickness & Minieres disease (more effective > atropine).
- **Preanesthesia medication** (no initial bradycardia).(adv over atropine)

II. Synthetic atropine substitutes (more selective → fewer side effects)

Better than atropine

1. Mydriatic cycloplegics (cyclopentolate -tropicamide - homatropine):

Used in

- **Iridocyclitis**; alternating with miotics to prevent synechia**. (so that the iris move all the time)**
- To **measure refractive errors (in order to examine the lens we need mydriasis so we use atropine)**
- For **fundus examination**.

Advantages : **shorter acting** than atropine → action is easier to reverse

→ preferred to atropine (except in children).

2. Antisecretory& antispasmodics: on GIT

- **Hyoscine butyl-bromide** (hyoscine only is natural **focus)
  : antispasmodic in renal, biliary & intestinal colic & in irritable bowel syndrome**.**
- **Dicyclomine, Pirenzepine (know this drug name)**
  ; selective M_1 blocker → **antispasmodic, Peptic ulcer**.

3. Urinary atropine substitutes:

- **Oxybutynin**: used in **nocturnal enuresis** & in **urine incontinence**.

4. Anti-parkinsonian (**benztropine - benzhexol**): Used in

- Drug induced parkinsonism
- Adjuvants in Parkinsonism presenting with tremors & to control sialorrhea.

5. Bronchial atropine substitutes

Ipratropium (non selective M_2 / M_3 blocker)

- **Inhaled** bronchodilator (M_3 blocker)
- **Advantages over atropine:**

  1- Poor CNS penetration

  2- No systemic atropine side effects

  3- No ↓ in mucociliary clearance of bronchial epithelium.

It is assumed that atropine decreases epithelial ciliary movement

- **Differences between ipratropium & inhaled β_2 agonist(bronchodilators)**
  These are ipratropium differences compared to b2 agonists::

  1- Gradual onset & late peak (40-60 min)

  2- Suitable for regular prophylactic use > rapid symptomatic relief

Both can be used in acute attacks but if I want to choose one it will be b2 agonist

- Used in **asthma & COPD (more effective in COPD > asthma** because the parasympathetic tone is the major factor in COPD).

- **Tolerance** develops due to block of presynaptic M_2 receptor →↑ ACh.

  Remember again that presynaptic M2 is inhibitory so when u block it ACH increases and tolerance develops ^^

- **A/E (transient):** dryness of mouth, tracheal irritation, cough, bad taste

  (because it is inhalation via mouth)

Tiotropium (selective M_3 blocker)

- **Longer acting** than ipratropium → used once/d;
- For maintenance in **COPD**. (not bronchial asthma)
- Does not block M_2 receptors → **no tolerance**.

Drugs with Atropine-Like Action

- Antiarrhythmics: quinidine - procainamide.
- Antihistamines (1st generation).
- Tricyclic antidepressants – antipsychotics– pethidine.
- Atropine substitutes. Know just the 2 groups that are highlighted

GANGLIONIC STIMULANTS

Imp The dr said to read it by ourselves because it is an easy topic (STILL INCLUDED) So I will highlight the things that he read

For a starter … here we are talking about the autonomic ganglia which is stimulated via nicotine in SMALL doses

Nicotine (small dose)

Mechanism of action:

1. Small dose →ganglionic stimulants (large dose→ blocker)
2. ↑Release of catecholamine from adrenal medulla
3. Act on Nn in CNS

Actions: depend on predominant tone

- **CVS:** Tachycardia – hypertension – VC of all vessels (except skeletal muscle and coronary) the sympathetic system has the upper hand
- **Blood:** ↑ Fatty acid concentration & platelet aggregation
- **GIT:** ↑ motility the parasympathetic system has the upper hand
- **CNS:** ↑ CTZ, ADH, CNS stimulation
- **Enzyme inducer**

Effects of chronic tobacco smoking:

- **GIT:** Salivation, inhibition of hunger pain
- **CVS:** Extrasystole, Atherosclerosis, Angina pectoris
- **Respiratory:** Cancer lung and larynx – nasopharyngeal and bronchial irritation

- **Eye:** Spasm of retinal vessels
- **Pregnancy:** ↑ incidence of abortion and neonatal mortality

Drugs used in smoking cessation:

1. **Nicotine replacement therapy**: gum, inhaler, patch

   (Give nicotine in small amounts and then stop it gradually)
2. **Bupropion (we took it in CNS)**
3. **Vareniciline (dr said it is not imp ^^)**

- direct Nn partial agonist
- reduce craving for tobacco

GANGLIONIC BLOCKERS

#Only used is **Trimetaphan**→ ultrashort acting ganglion blocker and direct VD

Block N receptor in the autonomic ganglia either Parasympathetic or Sympathetic

#Uses: **IV in - Hypertensive emergency –**

controlled hypotension in surgery

(in plastic and neurosurgery it is very imp not to have blood around while performing surgery in order the surgeon can see well)

Best of wishes wateen <3