Lecture 4: CHOLINERGIC SYSTEM (Parasympathetic Nervous System) AND DRUGS

Anticholinergic drugs (Cholinoceptor-Blocking Drugs)

ANTICHOLINERGIC DRUGS (PARASYMPATHOLYTICS = Cholinolytics = Cholinoceptor-blocking drugs = Cholinoceptor antagonists) are divided on the basis of their specific receptor affinities into:

- muscarinic antagonists (Muscarinic Receptor Antagonist = Atropinic Drugs = muscarinic receptor-blocking drugs = ANTIMUSCARINICS);
- nicotinic antagonists (antagonists of nicotinic receptors or nicotinic receptor-blocking drugs), which are divided into:
  - antagonists of Nn receptors (ganglionic blockers = GANGLIOPLEGICS);
  - antagonists of Nm receptors (NEUROMUSCULAR BLOCKING DRUGS = skeletal muscle relaxants = curare like substances).

Anticholinergic drugs are called parasympatholytic or cholinolytics because they block the effects of parasympathetic autonomic system.
I. ANTIMUSCARINICS

Antimuscarinics (muscarinic antagonists) have some effects that are not predictable from block of the parasympathetic nervous system.

Atropine (Hyoscyamine) is found in the plant *Atropa belladonna* (deadly nightshade) and in *Datura stramonium* (known as jimsonweed or Jamestown weed or sacred Datura, or thorn apple), Scopolamine (Hyoscine) is found in the plant *Hyoscyamus niger*, or henbane.

Classification

1. Natural antimuscarinic drugs:
   - **Atropine** (Hyoscyamine),
   - **Scopolamine** (Hyoscine).

2. Semisynthetic and synthetic derivatives:

   2.1. *Antimuscarinic drugs used in gastrointestinal and genitourinary disorders*
       - **antispasmodics** (reduce tone and motility of gastrointestinal and genitourinary smooth muscle):
         - quaternary amines:
           - antispasmodic properties: Propantheline, Butylscopolamine, Glycopyrrolate, Clidinium, Tridihexethyl, Anisotropine, Isopropamide, Methantheline, Oxyphenonium, Methylscopolamine, Hexociclim
           - overactive urinary bladder disease: Trospium, Emepronium
         - tertiary amines:
           - antispasmodic properties: Dicyclomine, Mebeverine, Oxyphencyclimine
           - overactive urinary bladder disease:
             - non-selective: Oxybutynin, Tolterodine, Propiverine, Flavoxate,
             - selective on M3: Darifenacin,
             - selective on M1, M3: Solifenacin
       - **antiulcus drugs**:
         - Pirenzepine (tertiary amine, selective on M1)
         - Telenzepine (quaternary amine, selective on M1)
         - Mepenzolate

   2.2. **Antiasthmatics**:
       - short action: Ipratropium, Oxitropium
       - long action: Tiotropium

   2.3. **Antiparkinsonians** (central M-cholinolytics)
       - Parkinson’ disease: Benztropine
       - drug-induced parkinsonism: Trihexyphenidyl, Biperiden, Orphenadrine, Procyclidine, Dipheniclimine

   2.5. **Mydriatics**: Homatropine, Cyclopentolate, Tropicamide

   2.6. **Centrally acting skeletal muscle relaxants** (used to treat acute local skeletal muscle spasm): Chlorzoxazone, Orphenadrine, Cyclobenzaprine, Carisoprodol, Chlorphenesin, Metaxolone, Methocarbamol

   2.7. **Drugs used to treat acute local skeletal muscle spasm and generalized spastic disorders**:
       - botulinum toxin type A and B.
**ATROPINE**

**Mechanism of action**
Atropine causes reversible blockade of cholinomimetic actions at muscarinic receptors. Atropine has high affinity for muscarinic receptors and it is not selective on muscarinic receptors (does not distinguish between subgroups of muscarinic receptors).

This mechanism explains the use as antidote in organophosphate intoxication or muscarine intoxication.

This mechanism explains the use in small doses as adjuncts to treatment of myasthenia gravis.

**Pharmacodynamic effects**

1. **Cardiovascular System:**
   - Heart: tachycardia by blocking vagal effects on M2 receptors on the SA nodal pacemaker (there is an initial bradycardia before the effects of peripheral vagal block become manifest).
     This effect is useful in the treatment of bradycardia, asystolia.
     This effect explains tachycardia as adverse effects and the contraindication in coronary atherosclerosis and in tachycardia (hyperthyroidism, cardiac insufficiency).
   - Blood vessels: at toxic doses, and in some individuals at normal doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. The mechanism is unknown. There is little effect on blood pressure.
2. **Smooth muscle (gastro-intestinal, genito-urinary, bronchial):**
   - antispasmodic agents (decrease the normal tone and amplitude of contractions) - this effect usually is not sufficient to overcome or prevent the marked spasm. Intestinal "paralysis" induced by antimuscarinic drugs is temporary; local mechanisms within the enteric nervous system will usually reestablish at least some peristalsis after 1–3 days of antimuscarinic drug therapy.
     This action is useful in the treatment of intestinal hypertonicity and hypermotility, of the spasm of biliary and ureteral colic. Alternative drugs from synthetic compounds are Propantheline, Butilscolopolamine, Glycopyrrolate, Clidinium, Dicyclomine, Mebeverine.
     This effect explains constipation as adverse effects (this effect is temporary – maximum 3 days).
   - increase the normal tone of sphincters
     This effect is useful in the treatment of urinary incontinence, but for this indication are preferred synthetic derivatives such as Trospium, Emepronium, Oxybutynin, Tolterodine, Propiverine, Darifenacin, Solifenacin.
     This effect explains acute urinary retention as adverse effects and the contraindication in prostatic hyperplasia.
   - bronchodilation in persons with asthma.
     This effect is useful as adjuncts to treatment of recent bronchial asthma and for chronic obstructive pulmonary disease. For this indication are preferred synthetic derivatives such as Ipratropium, Oxitropium, Tiotropium.
3. **Eye:**
   - cycloplegia (or paralyze the ciliary muscle): results in loss of the ability to accommodate, so eye cannot focus for near vision.
   - mydriasis (pupillary dilation): results in photophobia and blurring near vision. Conventional systemic doses of atropine have little ocular effect (48 – 72 hours), locally applied atropine produces ocular effects for 7 to 12 days.
These effects are useful in the treatment of iritis, irido-cyclitis; prevent adhesion between iris and lens or iris and cornea (therapeutic mydriasis). Alternative drugs from synthetic compounds is Homatropine.

These effects explain elevation of intraocular pressure, blurred vision and photophobia as adverse effects and the contraindications in glaucoma and for drivers.

4. exocrine glands → reduction of secretion:
- lacrimal glands: reduction of secretion → patients complain of dry or "sandy" eyes;
  This effect explains dry or "sandy" eyes as adverse effects.
- salivary glands: reduction of secretion → patients complain of dry mouth, and swallowing and talking may become difficult;
  This effect is useful in preanesthetic medication (especially in surgical interventions in buco-pharingean area).
  This effect explains dry mouth, and swallowing and talking difficulties as adverse effects.
- digestive glands: gastric secretions is markedly reduced, but the concentration of acid is not necessarily lowered because secretion of $\text{HCO}_3^-$ as well as of $\text{H}^+$, of mucin and of proteolytic enzymes is blocked;
  This effect explains the contraindication in chronic gastric ulcer.
- sweat glands: reduction of secretion → patients complain of dry skin. In adults, sweating is depressed enough to raise the body temperature, but only after large doses or at high environmental temperatures. In children, even ordinary doses may cause "atropine fever".
  This effect is useful in preanesthetic medication.
  This effect explains dry skin and atropine fever in children as adverse effects and the caution to avoid sun exposure.
- bronchial glands: reduction of secretion → dry the mucous membranes of the respiratory tract and increase the viscosity of secretions;
  This effect is useful in preanesthetic medication (for intubation).
  This effect explains dry mucous as adverse effects and the contraindication in severe bronchial asthma.

5. CNS:
- excitatory effects on CNS (with toxic doses of atropine, central excitation becomes more prominent, leading to restlessness, irritability, restlessness, excitement, disorientation, hallucinations, delirium);
  This effect is useful in preanesthetic medication (especially in surgical interventions in buco-pharingean area).
  This effect explains the contraindication in infants and elderly.
- antiemetic effect;
  This effect is useful in therapy (much less effective after severe nausea or vomiting has developed).
- adjuncts to treatment of Parkinson disease or parkinsonism;
  This effect is useful as adjuncts to treatment of Parkinson disease or parkinsonism.
  Alternative drugs from synthetic compounds are Benztropine, Trihexyphenidyl, Biperiden, Orphenadrine.
- spinal cord: block the spinal cord intercalary neuron receptors → skeletal muscle relaxation.
  This effect is useful in acute local skeletal muscle spasm, but for this indication are prefered synthetic derivatives such as Chlorzoxazole, Orphenadrine, Cyclobenzaprine.
Pharmacokinetics
- absorption: rapidly after oral or mucosal (conjunctival) administration;
- distribution: wide in whole body, bypasses blood-brain barrier, penetrate the conjunctiva of the eye;
- metabolism: partially in the liver
- elimination: metabolism in the liver, 60% is eliminated unchanged through kidney.
- $t_{1/2} = 2$ hours.
The effect of atropine declines rapidly in all organs except the eye (effects on the iris and ciliary muscle persist for 72 hours). Accommodation and pupillary reflexes are not fully recover for 7–12 days.

Indications:
- antidote in organophosphate intoxication or muscarine intoxication;
- antispasmodic agent (intestinal hypertonicity and hypermotility, biliary colicative pain);
- therapeautic mydriasis;
- severe bradicardia (initial treatment of patients with acute myocardial infarction in whom excessive vagal tone causes sinus or nodal bradycardia, reduce the severe bradycardia and syncope associated with a hyperactive carotid sinus reflex, eliminate premature ventricular contractions associated with a very slow atrial rate, reduce the degree of AV block when due to increased vagal tone), asystolia (if necessary, but after administration of Adrenaline);
- antiemetic effect;
- preanesthetic medication (especially in surgical interventions in buco-pharingean area),
- adjuncts to treatment of:
  - Parkinson disease or parkinsonism;
  - recent bronchial asthma;
  - myasthenia gravis;
- hyperhidrosis;
- alternative for the treatment of intracranial hypertension.

Adverse effects:
- dry mouth, dry skin, dry or "sandy" eyes;
- blurred vision and photophobia, mydriasis;
- elevation of intraocular pressure;
- palpitations, tachycardia;
- acute urinary retention;
- constipation.

Contraindications:
- glaucoma;
- prostatic hyperplasia;
- chronic gastric ulcer;
- coronary atherosclerosis, tachycardia (hyperthyroidism, cardiac insufficiency)
- infants, elderly;
- drivers.

Cautions: Avoid sun exposure. Avoid combining atropine with other drugs capable of causing muscarinic blockade.
Acute intoxication:
- antidote is Pilocarpine or Neostigmine.

SCOPOLAMINE
Mechanism of action – see Atropine.

Pharmacodynamics
- similar effects to Atropine, but the effects are stronger on salivary and bronchial secretion and on eye, and weaker on heart and abdominal organs;
- effects on CNS are different compared to Atropine:
  - therapeutic doses normally causes CNS depression: drowsiness, sedation, amnesia (block short-term memory), fatigue, dreamless sleep, with a reduction in rapid eye movement (REM) sleep.
  - antiemetic effect;
  - This effect is useful in therapy (much less effective after severe nausea or vomiting has developed).
  - euphoria.

Indications:
- antiemetic drug (drug of choice for nausea associated with motion sickness; useful for postoperative nausea and vomiting);
- antispasmodic agent;
- preanesthetic medication and obstetric amnesia (usually given with analgesics);
- diagnostic for WPW (Wolff-Parkinson-White) syndrome.

Adverse effects: similar to Atropine (plus effects on CNS such as drowsiness, sedation, dizziness, confusion, fatigue).

Contraindications: similar to Atropine.

QUATERNARY AND TERTIARY AMINE ANTIMUSCARINIC AGENTS have been developed to produce more peripheral effects with reduced central nervous system effects. They are incompletely absorbed, do not penetrate blood-brain barrier and eye, have longer action and are slowly eliminated.

- **Propantheline, Butylscopolamine, Glycopyrrolate** and Clidinium (from quaternary amines), **Dicyclomine** and **Mebeverine** (from tertiary amines) are the most used for gastro-intestinal smooth muscle spasm.
- **Pirenzepine** (antagonist selective on M1 receptors) is indicated for peptic ulcer disease (potent effect in inhibiting gastric acid secretion, with low effects on other organs).
- **Trospium, Emepronium, Oxybutynin, Tolterodine, Propiverine** (non-selective), **Darifenacin** (antagonists selective on M3), **Solifenacin** (antagonists selective on M1 and M3) are indicated for treatment of overactive urinary bladder disease (urinary incontinence from meningomielocel, neurological disorders, enurezis).
• **Ipratropium, Oxitropium, Tiotropium** are indicated for recent bronchial asthma and for chronic obstructive pulmonary disease. Disadvantages: increase of viscosity of mucus.

• **Benztropine, Trihexyphenidyl, Orphenadrine, Biperiden** are antagonists of CNS muscarinic receptors and are indicated for Parkinson’ disease and for drug-induced parkinsonism (extrapyramidal side effects of antipsychotic drugs and of Reserpine).

• **Homatropine** is indicated for therapeutic mydriasis (iritis, irido-cyclitis, prevent adhesion between iris and lens or iris and cornea).

• **Cyclopentolate, Tropicamide** are indicated for diagnostic mydriasis (to facilitate fundoscopy).

• **Chlorzoxazone, Cyclobenzaprine, Orphenadrine** are antagonists of the spinal cord intercalary neuron receptors, indicated for indicated for the treatment of acute local skeletal muscle spasm.

**Adverse effects:** similar to Atropine.

**Contraindications:** similar to Atropine.

**BOTULINUM TOXIN TYPE A AND B**

**Mechanism of action:** inhibits release of acetylcholine at neuromuscular junction because vesicles cannot dock and fuse with membrane → results relaxation of skeletal muscles.

**Pharmacokinetics:** onset and duration of action: 1-4 days: mild change; 7-10 days or longer: maximal effect; 2-4 months: duration may vary.

**Indications** (local injections):
- acute local skeletal muscle spasm (spasmodic torticollis, blepharospasm, severe primary axillary hyperhidrosis, achalasia) and generalized spastic disorders (associated with injury or disease of the CNS),
- cosmetic surgeons (improvement of moderate to severe glabellar frown lines for ages 18-65).

**Adverse effects:**
- after injection into facial muscles: change in facial expression (e.g., ptosis), dry mouth, facial swelling, headache etc. Some patients may be unable to close the eyelid completely;
- after injection into neck muscles: dysphagia, paralysis of the vocal cords, weakness of the neck muscles;
- after injection into limbs: local and general weakness;
- antibody formation (explains resistance to treatment);
- muscle atrophy.

**Contraindications:**
- pregnant or lactating women;
- active infection at injection site;
- myasthenia gravis (and other generalised disorders of muscle activity).
II. GANGLIOPLEGICS

Antagonists of Nn receptors (ganglionic blockers)
Mechanism of action:
These drugs block the action of acetylcholine of both parasympathetic and sympathetic autonomic ganglia. They are used in pharmacologic and physiologic research because they can block all autonomic outflows. They have limited clinical use.

Classification:
- Quaternary ammonium compounds: Hexamethonium, Pentolinium;
- Secondary amines: Mecamylamine;
- Tertiary amines: Pempidine;
- Monosulfonium compound: Trimethaphan.

Pharmacodynamic effects
1. Cardio-vascular system:
   - heart: tachycardia, decrease of force of contraction
   - blood vessels: vasodilatation (postural and exercise hypotension and syncope because both peripheral vascular resistance and venous return are decreased)
2. Gastro-intestinal tract:
   - decreased motility
   - weak decrease of glands secretion
3. Genito-urinary tract:
   - decreased motility and tone of bladder
   - impaired sexual function: inhibition of erection and of ejaculation
4. Eye
   - cycloplegia
   - moderate mydriasis
5. CNS
   - quaternary agents and Trimethaphan don’t cross the blood-brain barrier
   - Mecamylamine crosses easily the blood-brain barrier: determines sedation, tremor, choreiform movements, mental aberrations
6. Other organs:
   - salivary glands: inhibition of salivation
   - sweet glands: inhibition of secretion

TRIMETHAPHAN (Sodium nitroprusside is now preferred)
Indications:
- to produce controlled hypotension (to reduce bleeding in the operative field in neurosurgery).
- hypertensive emergencies (including pulmonary edema, dissecting aortic aneurysm);

Adverse effects:
- postural and exercise hypotension, syncope, impaired sexual function;
- constipation, urinary retention, attack of glaucoma, blurring of near vision, dryness of mouth, inhibition of sweating;
- allergic reactions due to the release of histamine.
III. NEUROMUSCULAR BLOCKING DRUGS

Antagonists of Nm receptors (=skeletal muscle relaxants = curare like substances)
These drugs block nicotinic receptors → result inhibition of Na⁺ channels and excitatory postsynaptic potential. Blockade of end plate function is accomplished by two basic mechanisms:
- blockade produced by drugs prevent access of the transmitter Ach to its receptor and thereby prevent depolarization (these are nondepolarizing blockers = competitive blockers = pachycurare);
- blockade produced by an excess of a depolarizing agonist such as acetylcholine (these are depolarizing blockers = leptocurare).

Classification
1. nondepolarizing neuromuscular blocking drugs:
   - long acting: - isoquinoline derivatives: D-Tubocurarine, Doxacurium, Metocurine
     - steroid derivatives: Pancuronium, Pipecuronium
     - other structure: Gallamine
   - intermediate acting: - isoquinoline derivatives: Atracurium, Cisatracurium
     - steroid derivatives: Vecuronium, Rocuronium
   - short acting: isoquinoline derivatives: Mivacurium
2. depolarizing neuromuscular blocking drugs:
   - ultrashort acting: Succinylcholine (Suxamethonium).

1. NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Mechanism of action:
- these are competitive antagonists for nicotinic Nm receptor (this receptor consists of 5 subunits surrounding a Na⁺-Ach-dependent channel). They close the Na⁺ channels found in open position. Ach from nerve ending is not able to combine with Nm receptor to generate end-plate potential, but increasing the concentration of Ach in the synaptic cleft consecutive to the administration of cholinesterase inhibitors may reverse the effect of these drugs.

Pharmacokinetics
- all have onium group (are administered only parenteral);
- muscles with higher blood flow receive more drug and are affected earlier;
- metabolism: - Gallamine is not metabolized
  - metabolised in the liver: D-Tubocurarine, Doxacurium, Metocurine, Pancuronium, Pipecuronium; Rocuronium, Vecuronium, Mivacurium;
  - Atracurium, Cisatracurium: undergoes non-enzymatic metabolism (Hoffmann elimination) which is independent of liver and kidney function
- elimination: for unchanged drug – in urine and bile.

Indications: skeletal muscle relaxation for:
- surgery
- laryngoscopy, bronchoscopy, esophagoscopy,
- reduction of fractures and dislocations
- electroconvulsive therapy

Contraindications: glaucoma, eye surgery, myotonic disease.

Advantages: cholinesterase inhibitors are antidote for the case of over-dosage: Neostigmine, Piridostigmine, Ambenonium, Physostigmine. Vecuronium is cardiovascular stable (it is of choice in cardiac patient).
Adverse effects and disadvantages:
- release of histamine (cause skin flushing, hypotension, tachycardia, bronchospasm, rarely anaphylactoid reaction):
  - moderate release for D-Tubocurarine and Mivacurium
  - slight release for Atracurium and Metocurine
- ganglionic blockade (cause arterial hypotension): D-Tubocurarine and Metocurine
- cardiovascular action by blocking of M2 receptors (determines tachycardia):
  - strong effects: Gallamine;
  - moderate effect: Pancuronium;
  - slight effect: Rocuronium;
- D-Tubocurarine decrease blood coagulability.

2. DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Mechanism of action:
- the molecule is similar to Ach, but persist longer in the synaptic cleft;
- these are partial agonists of Nm receptors. They open the Na+ Ach-dependent channel associated with Nm receptor → result depolarization of receptor. Initially it is produced skeletal muscle fasciculation, but the continue binding to receptor blocks the transmitting of further impulses → the initial end plate depolarization decreases and the membrane become repolarized. The membrane cannot easily be depolarized again because it is desensitized. The channels behave as if they are in a prolonged closed state, which result in a flaccid paralysis.

Indications:
- endotracheal intubation;
- electroconvulsive therapy.

Adverse effects:
- hyperpotasemia;
- malignant hyperthermia;
- postoperative muscle pain;
- increased intraocular pressure.

Contraindications:
- hyperpotasemia (renal failure, arrhythmias, skeletal muscle paresis, severe burns, severe sepsis);
- glaucoma;
- prolonged immobilization;
- low plasma cholinesterase activity;
- myotonic disease.

Advantages:
- rapid and short action effect;
- very good glotic relaxation.

Disadvantages:
- has no antidote;
- postoperative muscle pain;
- slight release of histamine;
- ganglionic blockade;
- cardiovascular action by stimulation of M2 receptors (negative inotropic and chronotropic responses).