ANTICHOLINERGIC DRUGS AND DRUGS ACTING ON AUTONOMIC GANGLIA

Smolensk state medical academy
Pharmacology department

ANTICHOLINERGIC DRUGS (Muscarinic receptor antagonists, Atropinics, Parasympatholytics)

- Conventionally, the term "anticholinergic drugs" is restricted to those which block actions of Ach on autonomic effectors and in the CNS exerted through muscarinic receptors.
- Though nicotinic receptor antagonists also block certain actions of Ach, they are generally reffered to as "ganglion blockers" and "neuromuscular blockers.

Classification of anticholinergic drugs

1. **M, N - cholinergic blockers**
2. **M – cholinergic blockers (antimuscarinic drugs)**
3. **N – cholinergic blockers:**

- ✔ *Neuromuscular blocking agents (skeletal muscle relaxant) - block Nm receptor*
- ✔ *Ganglion blockers - block Nn receptors*

Classification of cholinergic blockers

I. **M, N - c h o l i n o b l o c k e r s:**

- Aprofene

II. **M – c h o l i n o b l o c k e r s (Muscarinic receptor antagonists, Atropinics):**

1. **Natural alkaloids**

- Atropine sulfate
- Hyoscine hydrobromide (Scopolamine)
- Platyphylline hydrotartrate

Muscarinic receptor antagonists

2. Semisynthetic derivatives

- Homatropine hydrobromide
- Atropine methonitrate
- Hyoscine butyl bromide
- Ipratropium bromide (atrovent)
- Tiotropium bromide

Muscarinic receptor antagonists

3. Synthetic compounds

***Mydriatics*: Cyclopentolate, Tropicamide**

Antisecretory-antispasmodics:

- *Quaternary compounds:* Propantheline, Oxyphenonium, Clidinium, Pipenzolate methylbromide, Isopropamide, Glycopyrrolate
- *Tertiary amines:* Dicyclomine, Valethamate, Pirenzepine

Muscarinic receptor antagonists

- ***Vasicoselective:*** Oxybutinine, Flavoxate, Tolterodine
- ***Antiparkinsonian:*** Trihexyphenidyl, Procyclidine, Biperiden

Classification of anticholinergic drugs

N – c h o l i n o b l o c k e r s

I. Neuromuscular blockers(skeletal muscle relaxants)

Depolarizing ones

- *Short-term acting (5-10 min)*
  - **Suxamethonium cloride**

Neuromuscular blocking agents (skeletal muscle relaxants)

Non-depolarizing (anti-depolarizing) muscle relaxant of competitive type action

- *Short-term acting (15-20 min)*
- **Mivacurium chloride**
- *Mid-term acting (30-60 min):*
- **Alcuronium chloride**
- **Atracurium besilate**
- **Vecuronium bromide**
- **Cisatracirium besilate**
- **Rocuronium bromide**

Neuromuscular blocking agents (skeletal muscle relaxants)

- *Long-term acting (60-120 min)*
- Pancuronium bromide
- Pipecuronium bromide
- Tubocurarine chloride
- Mellictinum
- Doxacurium

Muscle relaxants of mixed action

- Dioxonium

Classification of anticholinergic drugs

Ganglion blockers (block Nn receptors):

- *Short-term acting ones (10-20 min)*
- Trepirium iodide
- Imechinum
- *Mid-term acting ones (3-4 hours)*
- Azamethonium bromide
- Hexamethonium benzosulfonate (benzohexonium)
- Pachycarpine hydroiodide
- *Long-term acting ones (8 hours and more)*
- Pempidine tosylate
- Temechinum

M-cholinoreceptors

- Block M-cholinoceptors and prevent from Ach action
- Inhibit activity of parasympathetic nervous system

The main pharmacological effects: of M-cholinoblockers

- ***Influence on eye function*:**

  as opposed to M-cholinomimetics:

- **dilate pupil (midriasis)**
- **paralyse (relax) accommodation**
- **increase intraocular tension**

- ***Influence on smooth muscles*:**

- **decrease tone of smooth muscles of GIT, bronchi, biliary and urinary tract**

- ***Action on the heart:***

- **tachycardia**
- **increase in atrio-ventricular conduction and myocardium oxygen demand**

The main pharmacological effects: of M-cholinoblockers

- *Influence on gland secretion* :

- the drugs inhibit secretion of glands due to block of M_3-cholinoceptors of glandular cell membranes
- Secretion of salivary, nasopharyngeal, bronchial, gastric, sweet and lachrymal glands decreases
- That leads to dryness of the skin and mucous membranes

The main pharmacological effects: of M-cholinoblockers

- ***Influence on thermoregulation***

- Block M_3-cholinoreceptors of sweet glands, inhibit sweet secretion what can lead to thermoregulation disturbance. As a result, body temperature can increase.

- ***Influence on the CNS***

- Preparations of tertiary structure (Atropine, Hyosyamine, Platyphyllin) pass through blood-brain barrier and take action on the CNS.
- At medium therapeutic dose Atropine blocks the relative cholinergic overactivity of basal ganglia, suppresses tremor and rigidity at parkinsonism.

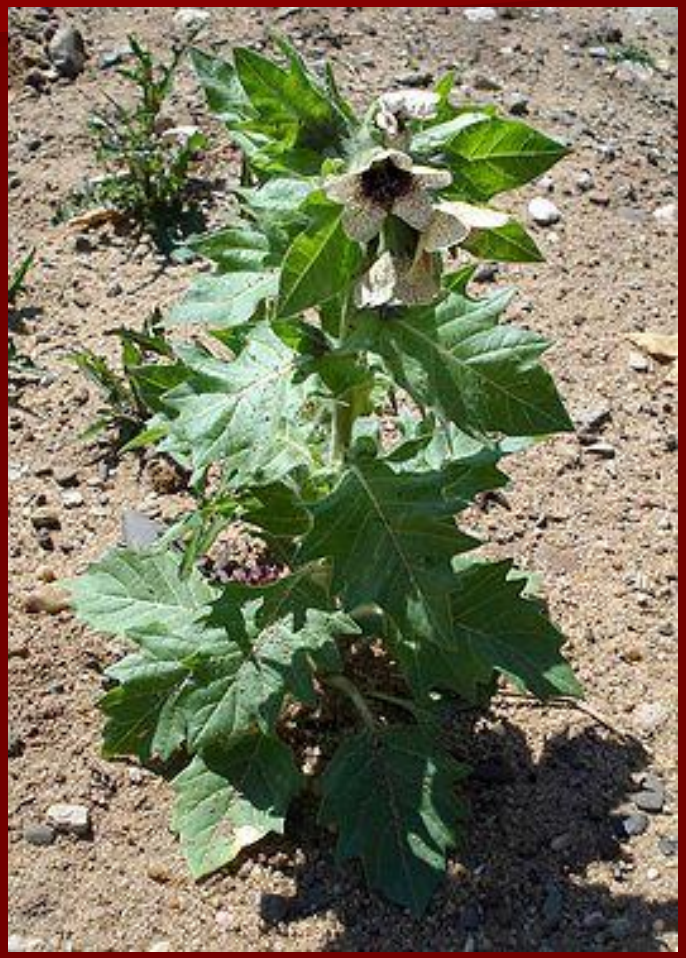
Comparative characteristics of M-cholinoblockers

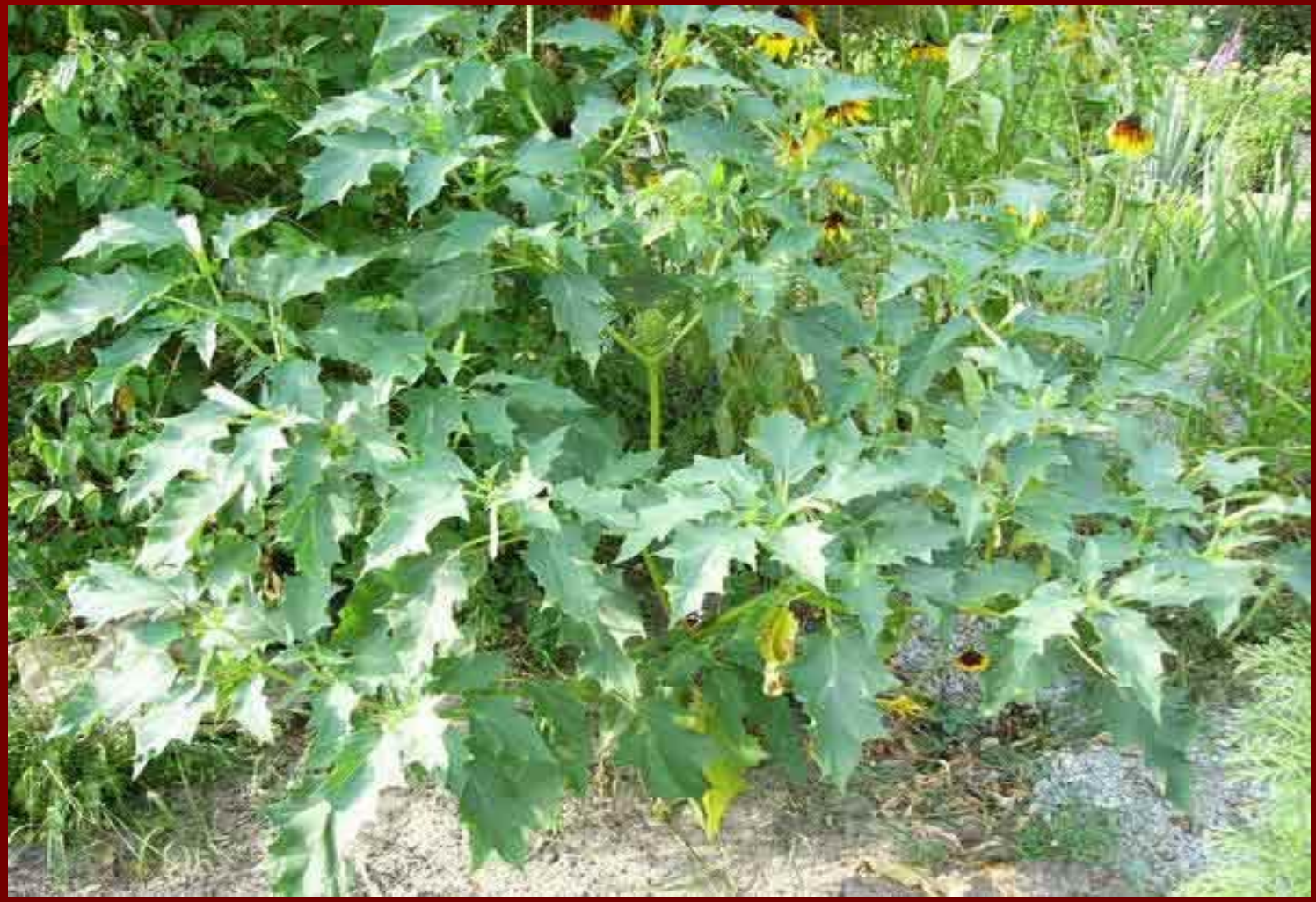
Atropine

- is an alkaloid contained in *belladonna*, *black henbane*, *datura* (thornapple, mad apple)
- It is well absorbed from GIT and from mucous membranes
- Duration of resorptive effect is about 6 hours
- Its biotransformation occurs in the liver
- it is mainly eliminated by kidney
- It is non-selective blocker of M-cholinoceptors
- At therapeutic doses it stimulates respiratory, vagal, vasomotor medullary centers

Belladonna

Black henbane





DATURA STRAMONIUM

Atropine

- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium, followed by respiratory depression and coma.

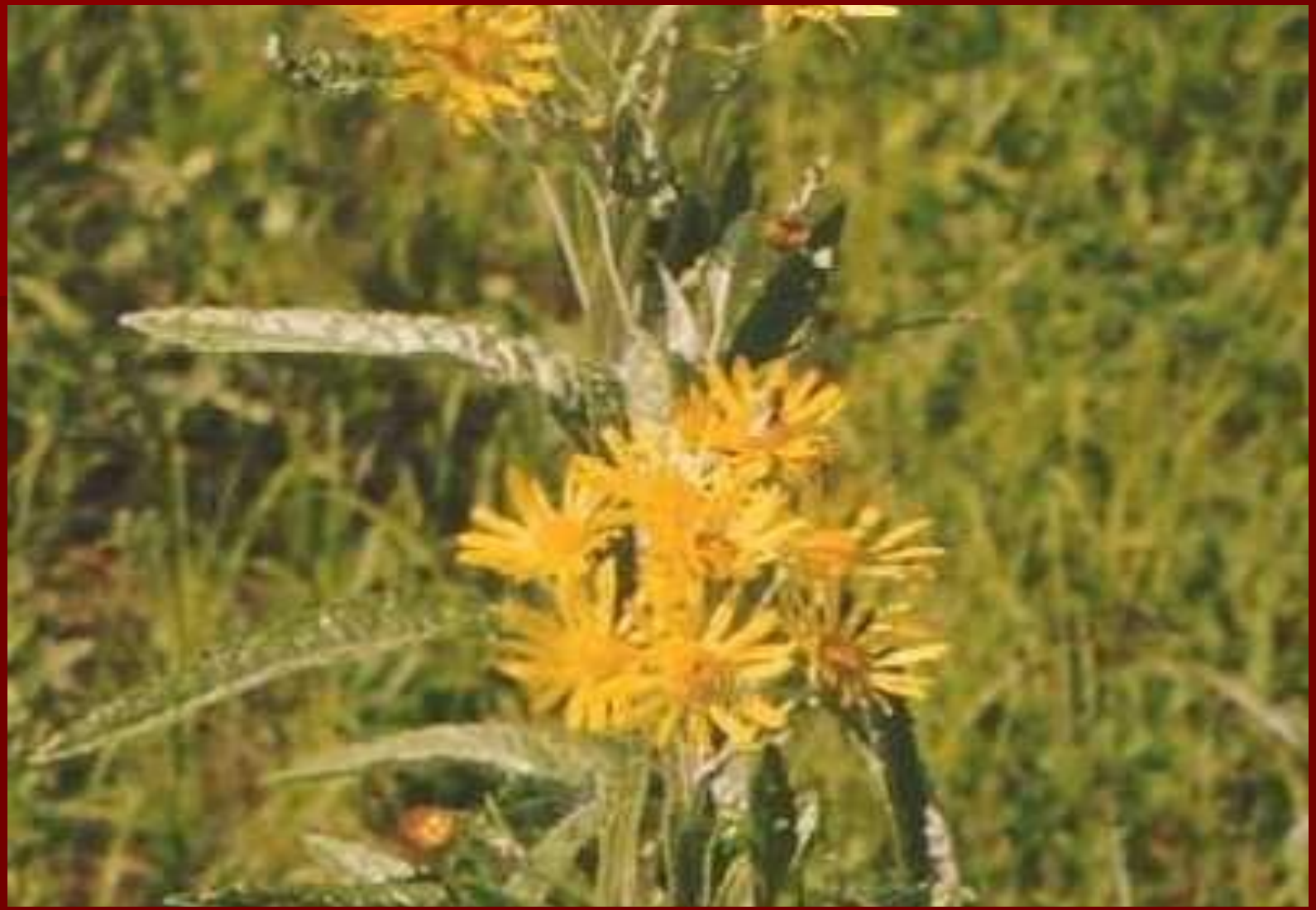
Comparative characteristics of M-cholinoblockers

Platyphyllin

- alkaloid, contained in plant groundsel
- It has “double” spasmolytic action:
- blocks м-cholinoreceptors, i.e. takes neurotropic spasmolytic action
- in contrast to other M-cholinoblockers it takes direct myotropic spasmolytic action

Scopolamine

- It is characterized by high activity regarding M-cholinoceptors of vestibular apparatus (antimotion sickness property due to depression of vestibular excitation)
- It takes depressant and amnestic action on the CNS, induces “twilight sleep” ans has been used as a *lie detector or truth serum*



Senecio (groundsel)

Comparative characteristics of M-cholinoblockers

Pirenzepine, Telenzepine

- Act selectively on M_1-cholinoreceptors of the stomach and inhibit gastric gland secretion of hydrochloric acid and pepsinogen

Ipratropium, Tiotropium

- Are quaternary atropinics
- they more markedly block M-cholinoceptors of smooth muscles of bronchi and cause their dilation

Indication for administration of M-cholinoblockers

1. ***For preanaesthetic medication*** (Atropine, Glycopyrrolate). They is used to inhibit bronchial secretion, to block vagal influence for prevention of reflex cardiac arrest and respiratory standstill
2. ***For elimination of spasms of smooth muscles of GIT, urinary tract , biliary tract*** more frequently Dicyclomine, Valethamate, Pipenzolate)
3. ***For relief of bronchospasm in COPD and bronchial asthma*** (Ipratropium, Tiotropium) by inhalation)
4. ***Stomach ulcer, hyperacid gastritis*** to inhibit secretion of HCl (Pirenzepine, Telenzepine, Propantheline)
5. ***Hyperkinesia, Parkinsonism*** (Trihexyphenidyl, Procyclidine, Biperiden)

Indications for administration of M-cholinoblockers

6. ***In ophthalmology***
- To dilate pupil for choice of eyeglasses, for examination of eye fundus (Tropicamide, Cyclopentholate, Homatropine)
- eye trauma, iridocyclitis (due to paralysis of accomodation and relaxation of circular muscle of eye pain decreases and healing is accelerated (Atropine)

7. ***Naupathia (motion sickness)*** – occurs in excitation of M-cholinoreceptors of vestibular apparatus (Scopolamine)
8. ***Poisoning with M-cholinomimetics and and anticholinesterases*** (Atropine)
9. ***In cardiology***
- Vagal cardiac arrhythmia
- Atrioventricular block (Atropine, synthetic analogues)

Indications for administration of M-cholinoblockers

10. *In urology* **(vasicoselective drugs)**

- For treatment of urinary incontinence (detrusor instability)
- renal colics (Oxybutinin, Dicyclomine, Flavoxate)

Adverse effects of M-cholinoblockers

- dry mouth
- dysphagia, speech disturbance (dysarthria)
- accomodation disorders
- tachycardia
- constipation
- urinary retention

Poisoning by atropine and atropinics

Clinical symptoms of acute poisonning:

- *dry flushed and hot skin, especially over face and neck*
- *hyperthermia,*
- *tachycardia, rapid («galloping») pulse,*
- *shining dilated pipils, accomodation paralysis (blurring of near vision), diplopia, photophobia, intraocular tension increase,*
- *dyspnea (tachypnea),*
- *headache,*
- *Dry mouth and throat, dysphagia, speech disturbance (dysarthria)*
- *Urinary retention,*
- *Excitement, psychotic behaviour, ataxia, delirium, dreadfull hallucinations*

Poisonning by atropine and its analogues

- in severe cases – convulsion with loss of consciousness, coma, hypotension;
- *Phase of excitement can be absent in children,*
- *poisoning is more dangerous for children;*
- approximate lethal dose of atropine and scopolamine for adults is more 100 мg, for children less 10 years of age – about 10 мg

Mesures of first aid in poisonning

1. *Removal of non-absorbed poison from GIT*

- gastric lavage with tannic acid, saline purgatives (MgSO4), activated charcoal

2. *"dilution" and elimination of poison from the blood*

- forced diuresis (i/v saline infusion+diuretic Furosemide)

3. *Administration of pharmacological antagonists: anticholinesterases of reversible action*

- Physostigmine, Galantamine. They promote accumulation of Ach, which displaces M-cholinoblockers from bond to receptor

4. *Symptomatic therapy: tranquilizers, sedatives; physical cooling;*

in respiratory impairments - artificial lung ventilation,

in tachycardia – β-adrenoblockers

Contraindications:

- glaucoma
- myocardium lesion, heart valvular defect, cardiac insufficiency
- hyperthermia
- hypertension and tachycardia

N-cholinoblockers

- block *nicotinic receptor*, as a result, they stop transmission of nerve impulses in corresponding synapses;
- *N-cholinoceptors are not homogeneous and unequally react to pharmacological analyzers;*
- thus, *N-cholinoceptors of skeletal muscles* are sensitive to *tubocurarin* and not blocked by hexamethonium;
- *N-cholinoreceptors of vegetative ganglions*, to the contrary, are blocked by *Hexamethonium* and not sensitive to tubocurarin;
- so, nicotitinic receptors of skeletal muscles are conditionally designated as *Nm-cholinoceptors;*
- Receptors of vegetative ganglion neurones – *Nn-cholinoceptors*

N-cholinoblockers

According to selectivity of action on this two types receptors preparations of N-cholinoblockers are divided into 2 groups:

- *Skeletal muscle relaxants*

(*block Nm-cholinoceptors*) *and*

- *Ganglion blockers*

(block Nn-cholinoceptors)

Ganglion blockers

- block Nn-cholinoceptors in autonomic ganglia of sympathetic and parasympathetic nervous system

Ganglionic blockers

Classification according to chemical structure:

- Quaternary ammonium compounds:

  Imechinum, Trepirium, Azamethonium, Hexamethonium

  - they are badly absorbed from GIT
  - they do not pass to the CNS

- Tertiary amines:

  Pachicarpine, Pempidine, Temechinum

  - they are absorbed from intestine
  - they pass through blood-brain barrier

Ganglion blockers

Classification according to duration of action:

- *Short-term acting (10-20 min)*
  - **Trepirium iodide (Hygronium)**
  - **Imechinum**

Used for controlled hypotension during operations to decrease loss of blood

- *Mid-term acting (1-4 hours)*
  - **Azamethonium bromide**
  - **Hexamethonium benzosulfonate**
  - **Pachicarpine hydroiodide**

used for relief of hypertensic crysis

- *Long-term acting (6-12 hours)*
  - **Pempidine**
  - **Temechinum**

Mechanism of ganglionic blocker action

- is related to block of Nn-cholinoceptors in synapses of vegetative ganglia, medulla of adrenals, sino-carotide zone
- the preparations block receptors in sympathetic and parasympathyic ganglia differently
- thus, Hexamethonium and Pempidine block ion channels, coupled to Nn-cholinoreceptors

Mechanism of ganglionic blocker action

- other preparations (Imecninum) block recognizing receptor sites
- as a result, ganglion blockers interrupt impulse transmission in ganglia
- impulse flow to nerve endings stops
- that results in a decrease of noradrenalin release in synapses of vessels
- adrenaline secretion in chromaffin cells of adrenal glands decreases
- block of parasympathetic ganglions leads to stoppage of impulses to smooth muscles of GIT, bronchi and glands.

Pharmacological effects of ganglion blockers

As a result of block of parasympathetic ganglia:

- arteries, veins, peripheral blood vessels are dilated,
- ABP decrease,
- t.p.r., pre- and afterload decrease,
- tissue microcirculation is improved,
- blood congestion in veins increases
- uterine tone increases

Pharmacological effects of ganglion blockers

As a result of block of parasympathetic ganglia:

- *a tone* and motility of smooth muscles decrease
- secretion of salivary, gastric, bronchial glands decrease
- block of reflex reactions

Nowadays ganglion blockers are used very seldom, as their action is nonselective and so they have many adverse effects

Adverse effects of ganglion blockers

- Orthostatic collapse (fall of arterial blood pressure)
  - Danger of thrombosis due to slowing-down of blood flow (stasis)
  - To prevent orthostatic collapse ganglion blockers must be injected in recumbent position and after introduction patient must stay recumbent for 2 hours
- Atony of intestine and urinary bladder,
- Constipation, urinary retention,
- Midriasis, paralysis of accomodation,
- Dry mouth, dysphagy, dysarthria (speech disturbance)

Contraindications:

- Hypotension
- Ischemic heart disease
- Glaucoma
- Liver and kidney function disorders

First aid in overdosage with ganglion blockers

- Introduction of pharmacological antagonists (anticholinesterases), analeptics
- Artificial lung ventilation (ALV)
- Orthostatic hypotension is releaved by introduction of vasoconstrictive agents (Norepinephrine, Phenylephrine)

Skeletal muscle relaxants (neuromuscular blockers)

- *Skeletal muscle relaxants (curare-like agents)* cause total relaxation of skeletal muscles due to selective block of

  Nm-cholinoceptors and stoppage of neuro-muscular transmission in neuro-muscular synapses – myoparalytic effect (paralysis of skeletal muscles)

Pharmacodynamics of muscle relaxants

Non-depolarizing (antidepolarizing) muscle relaxants

- Most of them act as competitive antagonists of Ach
- They block Nm-cholinoceptors of postsynaptic membrane of neuromuscular synapse and prevent depolarizing action of Ach
- Postsynaptic membrane at that stays non-depolarized
- Transmission of impulses from nerve endings to skeletal muscles is blocked, as a result, skeletal muscles are relaxed.

Depolarizing muscle relaxants

Suxamethonium chloride -

(doubled molecule of acetylcholine)

- interacts with Nm-cholinoreceptors of postsynaptic membrane, causes its stable depolarization
- desensitization (loss of sensitivity) of receptors and neuromuscular block occur
- A muscle contracts, then relaxes
- Microtrauma of fibers and muscle pains are observed in postoperative period

Depolarizing muscle relaxants

- Anticholineasterases potentiate (enhance) action of depolarizing muscle relaxats
- *Inactivation of depolarizing muscle relaxants is realized by pseudocholinesterase – butyrylcholinesterase of plood plasma*
- In overdosage of DMR transfusion of fresh donor blood can be recommended, but not anticholinestarase agents
- practically: Artificial lung ventilation (ALV) is performed, in 5-10‘ the drug is destroyed

Muscle relaxants of mixed action

- Dioxonium - *is seldom used*

  initially it acts like depolarizing muscle relaxants (cause depolarization of membrane), then membrane potential is restored, but receptors are blocked for action of acetylcholine similar to antidepolarizing muscle relaxants)

Administration of muscle relaxants

- *Anesthesiology and surgery:*

  they used for relaxation of skeletal muscles in reduction of dislocations, reposition of bone (fractured) fragments, intubation of trachea, endoscopy, laryngospasm, assisted ventillation (ALV)

- Convusions, severe cases of tetanus and status epilepticus
- Muscles are relaxed in certain order: *muscles of face and neck, extremities and trunk, respiratory muscles and diaphragm*

Muscle relaxants are used when ALV apparatus is available.

Administration of muscle relaxants

- They are quaternary ammonium compounds, and so they badly absorbed from GIT and used only intravenously
- A drug Mellictinum is tertiary base, it is a single muscle relaxant in the form of tablets.

  It decreases tone of skeletal muscles not producing their paralysis

Adverse effects of muscle relaxants

- *Depolarizing ones:*
  - cardiac arrhythmia, ABP rise
  - Muscle pains in postoperative period
  - ↑ intraocular tension and intracranial pressure, myoglobinemia, hyperkaliemia
- *Antidepolarizing ones:*
  - arterial hypotension,
  - bradycardia or tachycardia,
  - myocardium ischemia,
  - ventricular extrasystoles,
  - bronchospasm

Antagonists of muscle relaxants

- Neostigmine 0.5-2.0mg i.v., preceded by Atropine to block muscarinic effects, rapidly reverses paralysis induced by competitive neuromuscular blockers
- Sugammadex is new antagonist of antidepolarazing muscle relaxants. Its use does not need Atropine.