Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # : 9-Cholinergic Drugs

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SHEET

SLIDES

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Cholinergic Drugs

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Cholinergic Drugs

Cholinomimetics:

1. **Acetylcholine receptor stimulants: Agonists that stimulate acetylcholine muscarinic and nicotinic receptors.**

- **Muscarinic receptors are located on effector tissues (smooth muscle, heart & exocrine glands)**
- **Nicotinic receptors are located in autonomic ganglia.**

Cholinergic Drugs

2. **Cholinesterase inhibitors:**

   Drugs which inhibit the hydrolysis of endogenous acetylcholine leading to its accumulation at its receptors. The excess acetylcholine stimulates cholinoceptors (not selective) to evoke increased response.

Direct-Acting Cholinomimetics

1. **Choline esters: Acetylcholine, Methacholine, Carbachol, & Bethanechol.**
2. **Alkaloids (naturally occurring): Muscarine & Pilocarpine.**

Pharmacokinetics:

- **Choline esters are quaternary ammonium compounds, charged, highly water soluble and insoluble in lipids.**

Direct-Acting Cholinomimetics

- **They are poorly absorbed and poorly distributed into most tissues.**
- **They are hydrolyzed in the GIT and not active by the oral route.**
- **They differ in their susceptibility to hydrolysis by cholinesterase.**

Direct-Acting Cholinomimetics

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

Direct-Acting Cholinomimetics

- **The tertiary natural cholinomimetic alkaloid, pilocarpine, is well absorbed from most sites of administration.**
- **The alkaloid, muscarine is a quaternary amine and is less completely absorbed from GIT than tertiary amines, but is toxic when ingested.**

Direct-Acting Cholinomimetics

Pharmacodynamics:

- **Most of the direct organ-system effects of cholinomimetics can be predicted from knowledge of the effects of parasympathetic nerve stimulation and the distribution of muscarinic receptors.**

Direct-Acting Cholinomimetics

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength

Direct-Acting Cholinomimetics

Blood vessels	
Arteries	Dilation (via EDRF). Constriction (high-dose direct effect)
Veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

Direct-Acting Cholinomimetics

Eye:

1. **Contraction of the smooth muscle of the iris sphincter → miosis.**
2. **Contraction of the ciliary muscle → accommodation for near vision.**
3. **Facilitation of aqueous humor outflow into the canal of Schlemm, which drains the anterior chamber, and thus, reduces intraocular pressure.**

Direct-Acting Cholinomimetics

Cardiovascular System (M_2 receptors):

The direct effects of muscarinic receptors stimulants may be modified by homeostatic responses.

1. **Infusion of small doses of acetylcholine causes vasodilation, resulting in reduction of blood pressure.**

Direct-Acting Cholinomimetics

2. **Large doses of acetylcholine produce bradycardia (negative chronotropy)**
3. **Decreased AV node conduction velocity (negative dromotropy) and increased refractory period.**
4. **Decreased contractility of atrial muscle (negative inotropy), and decreased refractory period.**

Direct-Acting Cholinomimetics

5. **Effects on ventricles are much less than those on atria.**

   The effects of cholinomimetics are similar to those of acetylcholine. The main differences are in potency and duration of action (longer).

Direct-Acting Cholinomimetics

6. **Pilocarpine (IV) has different effects on blood pressure: after the initial reduction in blood pressure, hypertension occurs due to sympathetic ganglionic discharge caused by activation of postganglionic M_1 receptors.**

Direct-Acting Cholinomimetics

Respiratory System:

1. Contraction of smooth muscle of the bronchial tree.
2. Stimulation of secretions of glands in tracheobronchial mucosa.

Direct-Acting Cholinomimetics

Gastrointestinal Tract:

1. **Increased secretions of the gut. The salivary and gastric glands are strongly stimulated, while those of pancreas and small intestine less so.**
2. **Increased motor activity of the gut (M_3 receptors). Peristaltic activity is increased throughout the gut and most sphincters are relaxed.**

Direct-Acting Cholinomimetics

Genitourinary tract (M_3 receptors):

1. **Stimulation of detrusor muscle of the urinary bladder.**
2. **Relaxation of bladder sphincter.**

- **Both promote voiding (urination).**

3. **Human uterus is not sensitive to muscarinic agonists.**

Direct-Acting Cholinomimetics

Secretory glands:

1. **Stimulation of secretions of sweat, lacrimal and nasopharyngeal glands.**

Indirect-Acting Cholinomimetics

- **Also called acetylcholinesterase inhibitors or anticholinesterases.**
- **Include the following agents:**

1. **Edrophonium. Simple alcohol bearing a quaternary ammonium group.**

Indirect-Acting Cholinomimetics

2. **Carbamates:**

   Neostigmine. (ester of carbamic acid) and is a quaternary ammonium.

   Physostigmine. is a naturally occurring tertiary amine (lipid soluble).

   Carbaryl. Very high lipid solubility, insecticide.

Indirect-Acting Cholinomimetics

3. **Organophosphates:**

   Echothiophate (thiocholine derivative of clinical value), Parathion, Malathion → Paraoxon, Malaoxon (Insecticides) , Soman (nerve gas).

- **These compounds (Anticholinesterases) have similar pharmacodynamics but differ in chemical structure and pharmacokinetics.**
- **Some of them are insecticides.**

Indirect-Acting Cholinomimetics

Pharmacokinetics:

- **Absorption of quaternary carbamates from the conjunctiva, skin and lungs is poor. Oral doses are much higher than parenteral doses. Distribution into the central nervous system (CNS) is negligible.**

Indirect-Acting Cholinomimetics

- **Physostigmine, in contrast, is well absorbed from all sites and can be used topically. It is also distributed to the CNS (why?). It is more toxic than more polar carbamates.**

  Carbamates can be metabolized by cholinesterase and nonspecific esterases.

Indirect-Acting Cholinomimetics

- **The organophosphates (except echothiophate) are well absorbed from skin, lung, gut and conjunctiva. They are extensively distributed to all parts of the body including CNS.**
- **Echothiophate is highly polar and is used topically in the conjunctiva.**

Indirect-Acting Cholinomimetics

Pharmacodynamics:

- **Inhibition of cholinesterases increases the concentration of endogenous acetylcholine.**

1. **Edrophonium produces a short-lived (2-10 minutes) and reversible inhibition of the enzymes.**
2. **Carbamates produce a prolonged (0.5-6 hours) and reversible inhibition.**

Indirect-Acting Cholinomimetics

3. **Organophosphates phosphorylate the active site covalently and irreversibly. The effect is long-lasting (hundreds of hours). Later on, one oxygen-phosphorus bonds is broken leading to strengthening of the phosphorus-enzyme bond, a process called aging.**

Indirect-Acting Cholinomimetics

- **Oximes (pralidoxime) are nucleophiles and are able to break the phosphorus-enzyme bond before aging occurs, and are called “Cholinesterase regenerators”.**
- **They are part of the treatment of organophosphate but not carbamate poisoning.**
- **When? & Why?**

Indirect-Acting Cholinomimetics

- **Organ-system effects:**

  These effects are due to accumulation of acetylcholine at all cholinergic sites. Therefore, the actions are similar, but not identical, to those of the direct-acting cholinomimetic agonists.

1. **Actions on eye, GIT, respiratory tract and urinary tract are similar to the direct-acting cholinomimetic agonists.**

Indirect-Acting Cholinomimetics

2. **CNS (both muscarinic and nicotinic receptors):**

- **Low concentrations cause diffuse activation of CNS and a subjective alerting response.**
- **In higher concentrations, they produce generalized convulsions followed by coma and death.**

Indirect-Acting Cholinomimetics

3. CVS:

- **They can stimulate both parasympathetic and sympathetic ganglia (nicotinic receptors), although parasympathetic activation predominates.**
- **Sympathetic ganglia stimulation may counteract the effects of acetylcholine on vascular beds → vasoconstriction.**

Indirect-Acting Cholinomimetics

- **At toxic doses these agents may cause tachycardia, instead of bradycardia.**

4. **Neuromuscular junction (nicotinic receptors):**

- **Low concentration increases the strength of contraction in skeletal muscle.**

Indirect-Acting Cholinomimetics

- **High concentration leads to fibrillation of the muscle fibers, muscular fasciculation may also occur.**
- **Marked inhibition of acetylcholinesterase my produce neuromuscular blockade.**

Cholinomimetics

Therapeutic Uses:

A. Eye:

Glaucoma: These agents reduce intraocular pressure by facilitating outflow of aqueous humor (pilocarpine, methacholine, carbachol, physostigmine, echothiophate).

Cholinomimetics

B. Gastrointestinal and Urinary tracts:

1. Atony of bowel following surgery.

2. Postoperative urinary retention.

First exclude mechanical obstruction.

(neostigmine).

Cholinomimetics

C. Neuromuscular junction:

1. Myasthenia gravis: Edrophonium (diagnosis), pyridostigmine (treatment).

2. Antidotes for competitive neuromuscular junction blockers such as tubocurarine (neostigmine).

Cholinomimetics

D. Antimuscarinic drug (atropine) intoxication: Physostigmine counteracts both peripheral and central effects of atropine.

Cholinomimetics

Adverse effects:

1. **Nausea and vomiting**
2. **Diarrhea**
3. **Urinary urgency**
4. **Salivation**
5. **Lacrimation**

   (SLUD)
6. **Miosis**

Cholinomimetics

7. **Sweating**
8. **Cutaneous vasodilation → flushing.**
9. **Bronchoconstriction.**
10. **CNS effects (organophosphates)**

- **Antidote for all cholinomimetics is atropine.**
- **For organophosphates, pralidoxime may be used in addition (?).**