University of Mosul
Lecture No.: 5
College of Veterinary Medicine
Date:
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Website:

Lecture title: Parasympathomimetic drugs

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Summary:

Parasympathomimetic drugs (Cholinomimetics)

■ The parent compound of all cholinomimetic drugs is **acetylcholine**.

■ **ACh is the natural neurotransmitter in the following sites:**

− All autonomic ganglia whether sympathetic or parasympathetic.

− Parasympathetic nerve endings to involuntary organs and exocrine glands.

− Sympathetic nerve endings to thermoregulatory sweat glands.

− Sympathetic nerve endings to adrenal medulla.

− Skeletal muscle motor end plate.

− Certain tracts within the CNS

Ach is **not used clinically** because: (1) it has very short duration of action (seconds)due to rapid hydrolysis by AChE enzyme; and, (2) it lacks selectivity.

Classification of cholinomimetic drugs

Direct-acting cholinomimetics	Indirect-acting cholinomimetics
They act by **direct stimulation** of cholinergic receptors	They act by **inhibition of AChE enzyme** leading to accumulation of ACh.
■ **Muscarinic agonists** Bethanecol, carbachol, Pilocarpine, cevimeline	■ **Reversible ChE inhibitors:** Physostigmine, neostigmine, pyridostigmine, donepezil
■ **Nicotinic agonists** Nicotine, lobeline	■ **Irreversible ChE inhibitors:** Organophosphate compounds

DIRECT-ACTING PARASYMPATHOMIMETICS

Muscarinic agonist

Pharmacological effects:

1- CVS→ bradycardia (stimulation of M2)

2-B. V→M3 receptor are stimulated by external Ach through non innervated by NO formation → VD

3-GIT→ increase peristalsis (M3) increase HCl secretion (M1).

4- U. B→ contraction of wall and relaxation of sphincter (M3)

5- Uterus → contraction of non-pregnant uterus (M3)

6- Eye → miosis+ decrease IOP +accommodation for near vision (M3)

7- Bronchi → bronchial constriction and increase bronchial secretion (M3)

8-Exocrine glands → increase secretion, lacrimation, and salivation.

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1. Carbachol

 It is choline ester but resistant to hydrolysis by AChE enzyme.

 It stimulates both muscarinic and nicotinic receptors.

 It is used as local eye drops to ↓ IOP in glaucoma. It contracts the ciliary ms causing opening of the trabecular meshwork and facilitates drainage of aq humor**.**

2. Bethanechol

 It is a choline ester but resistant to hydrolysis by AChE enzyme, so it has long duration of action (2-3 h) as compared to Ach.

 It stimulates muscarinic receptors with **no activity on nicotinic receptors**.

 It is used to reverse post-operative urine retention and paralytic ileus (in absence of organic obstruction).

N.B.

 Bethanechol is administered **orally or s.c.,** not by i.v. or i.m., **because parenteral administration may cause cardiac arrest.**

 Bethanechol is contraindicated to treat urine retention due to mechanical obstruction of the bladder or intestine because increasing contraction against a closed outlet can lead to rupture of the viscus.

3. Cevimeline and pilocarpine

 Cevimeline is synthetic drug – pilocarpine is a natural plant alkaloid.

 Both drugs act as muscarinic agonists **with no nicotinic effects**.

 Both drugs can be given orally to **increase salivary secretion** and decrease symptoms of dry mouth (xerostomia) associated with Sjogren syndrome.

 Pilocarpine is used as local eye drops to ↓ IOP in glaucoma.

Adverse effect of muscarinic agonists

Most important side effects include nausea, vomiting, sweating, salivation, bronchoconstriction and diarrhea, all of which can be blocked by atropine.

Contraindication of muscarinic agonists:

1- Peptic ulcer.
2- Bronchial asthma

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Nicotinic Agonists

1-Nicotine

- At small dose activate N receptors but high dose blocks these receptors.
- Used in smoke cessation.
- Drugs form: chewing gum, lozenge, sublingual tablet, oral inhalator, patch and nasal spray.

2-Varenicline

- Partial agonist on N receptor.

- Used in smoking cessation
- Only as tablet form
- Contraindicated in pregnancy

Indirect acting parasympathomimetic(Cholinesterase inhibitors)

Mechanism of action: Drugs that prevent destroy of Ach by pseudocholinesterase and true cholinesterase resulting in accumulation of ACh and stimulation of both muscarinic and nicotinic receptors**.**

I-**Reversible - Indirect parasympathomimetic (carbamylation)**

They interact with AChE enzyme by making **reversible bond** allowing duration of inhibition lasting from minutes to hours.

Physostigmine

1- Neostigmine
2- Pyredostigmine
3- Edrophonium.
4- **Rivastigmine (treatment of Alzheimer's disease)**
5- **Donepezil (treatment of Alzheimer's disease)**

Physostigmine	**Neostigmine**
Plant alkaloids	Synthetic
Tertiary amine	Quaternary amine
Cross BBB	NOT
well-absorbed from the GIT	Not absorb orally
Central effects: headache, insomnia, excitation, and convulsions.	None
Uses:	Uses:
1- Glaucoma 2- Ruminal atony 3- Atropine poisoning.	1- Postoperative urine retention and Paralytic ileus 2- Ruminal atony 3- Myasthenia gravis 4- Muscle relaxant poisoning

Note:

1- In case of poisoning with physostigmine use atropine as antidote
2- Neostigmine has 2 mechanisms to treat myasthenia gravis

- ChE inhibitor →↑ACh
- Direct acting on NMJ →Nm receptor stimulant.

3- Neostigmine +atropine to block M receptors.
4- Edrophonium: more selective on NMJ but have short duration of action so it uses for diagnosis myasthenia gravis.
5- Pyridostigmine more selective on NMJ, not need atropine to block M receptors.

II-Irreversible - Indirect parasympathomimetic (phosphorylation)→ organophosphorus compound.

1- Insecticide: malathion, parathion.
2- Drug: Ecothiopate
3- Nerve gases: sarin and soman

- These compounds have very rapid of absorption (skin, orally and inhalation)
- At time passes, the strength of the bond increases, (a process called aging) and AChE become irreversibly inhibited (with most types of OP , 50% of the enzyme undergo aging after 3 hour and 95% after 12 hours).

Signs of poisoning

D: Diarrhea and colic.

U: Urination.

M: Miosis.

B: Bradycardia and Bronchospasm.

E: Emesis, Excitation of CNS.

L: lacrimation.

S: Salivations and Seating, Skeletal muscle twitches.

Treatment:

1. Atropine
2. Pralidoxime
3. Diazepam
4. Oxygen supply

Cholinergic antagonists

Muscarinic antagonists:

Actions and chemical structure

They are either tertiary amine alkaloids or quaternary amines:

- **Plant alkaloids:** atropine is found in *Atropa belladonna* and scopolamine (hyoscine) is found in *Hyoscyamus niger*. They are tertiary amines (i.e. well absorbed and can pass to **CNS**).
- **Synthetic derivatives:** are either tertiary or quaternary amines (limited **CNS** penetration):

- Drugs used mainly as **bronchodilators:** Ipratropium
- Drugs used mainly as **antispasmodics:** Hyoscine butylbromide
- Drugs used mainly to **decrease HCl secretion:** Pirenzepine
- Drugs used mainly for **cystitis:** Oxybutynin
- Drugs used mainly for **urine incontinence:** Tolterodine
- Drugs used mainly as **mydriatics:** Homatropine, tropicamide
- Drugs used mainly to treat **parkinsonism:** Benztropine

Mechanism and pharmacological effects

Muscarinic-receptor antagonists are **competitive antagonists** of ACh at all muscarinic receptors.

1-CVS effects

 They block M2 receptors in the SA node and **increase HR**.

2-Respiratory

 Bronchodilatation and decrease mucus secretion.

3-GIT

 Decrease salivation and HCl secretion.

 Decrease motility (antispasmodic action).

4-Urinary bladder

 Relaxation of the bladder smooth muscles and contraction of the sphincters leading to **urine retention**.

5-Sweat glands

 Blocking of muscarinic receptors in thermoregulatory sweat glands (cholinergic) leading to **dry skin** and elevation of body temperature **(atropine fever)**.

 Children are more sensitive to this effect.

6-Eye

 Passive **mydriasis** due to paralysis of constrictor pupillae muscle.

 Increase **IOP** due to mydriasis (decrease aqueous humor drainage).

7-CNS

 Tertiary amines can produce sedation, amnesia, delirium, and hallucinations.

has anti tremor effect in Parkinson disease due to blocking muscarinic receptor in brain →↓ Ach activity.

Uses

	Atropine	➢ Preanesthetic to reduce salivary and respiratory secretion. ➢ Treat anti – ChE Toxicity. ➢ Treat mushroom toxicity. ➢ Anti-diarrheal effect when it mixed with diphenoxylate

1	Hyoscine (M1) blocker	Motion sickness
2	Hyoscine butyl bromide (M3) blocker	Antispasmodic (colic)
3	Ipratropium (M3) blocker	Asthma
4	Tolterodine (M3) blocker	Urine incontinence (cystitis)
5	Homatropine (M3) blocker	Eye fundus examination
6	Benztropine (M1) blocker	Parkinson disease
7	Pirenzepine (M1) blocker	Peptic ulcer

Side effects

1- Blurred vision

2- Glaucoma

3- Dry of all body secretion

4-Urine retention

5-Tachycardia

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Anti-nicotinic agent s

I-Ganglionic blockers:

It's a type of drugs that inhibits transmission between preganglionic and postganglionic neurons in the ANS by acting as nicotinic receptors antagonist.

1- **Nicotine**: is an agonist Ach, but in high doses it blocks ganglia.
2- **Hexamethonium**
3- **Trimethaphan**
Because of lack of selectivity and **numerous adverse effects**, they are **used Rarely.**

II-Neuromuscular blockers

Competitive non- depolarizing agents

Agent

Tubocurarine (prototype) is rarely used clinically at this time.

■ Semisynthetic derivatives:

 Mivacurium

- Atracurium and Cisatracurium
- Vecuronium

Absorption and distribution:

- All neuromuscular blockers are quaternary amine (not cross BBB)
- not cross placenta
- all taken by injection route

Metabolism

- Atracurium: spontaneous plasma hydrolysis. Breakdown products may cause **seizures.**
- Vecuronium: liver.

Mechanism of action: Competitive antagonize N receptors at NMJ causing muscle relaxation. Muscle paralysis can be reversed by excess Ach (AChE inhibitors).

Adverse effect: Histamine release.

Contraindication:

1- Asthma.
2-mysthenia gravis.
3-with aminoglycosides, tetracycline and quinidine

Uses:

1- To induce muscle relaxation during surgical operation
2- To control convulsions during electroconvulsive therapy

Noncompetitive Depolarizing agents

Succinylcholine (Ach-Ach) suxamethonium

Mechanism of Action

Depolarizing block of **Nm** receptors → ms paralysis through **2 phases:**

- **Phase 1:** initial depolarization → transient ms contraction followed by paralysis due to maintained depolarization
- **Phase II:** the muscle become repolarized again but remains insensitive to stimulation by Ach.

Metabolism:

By plasma pseudocholinesterase enzyme

Adverse effects:

1- Muscarinic signs

2-Malignant hyperthermia: persistent Na channel opening→↑Na → trigger release of Ca from endoplasmic reticulum →↑oxidative metabolism---- fever
3- Hyperkalemia: cardiac arrhythmia and cardiac arrest.
4-Postoperative muscle pain.
5- Increase IOP due to increase contraction of extraocular muscle.

Contraindication

1-Peptic ulcer
2- Patient with pseudocholinesterase deficiency.
3-Glucoma

Notes:

- Succinylcholine has short duration of action in horses because high level of pseudocholinesterase
- Dangerous in ruminant because of low level of pseudocholinesterase.
- ChE inhibitors potentiate the action of succinylcholine.

Muscle relaxant:

Classification

1- **Central muscle relaxant.**
2- **Peripheral muscle relaxant.**
3- **Direct acting M relaxant as dantrolene.**

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Central muscle relaxant:

They inhibit spinal and supraspinal polysynaptic pathways → decrease skeletal muscle tone.

1- Benzodiazepines and Barbiturates: bind to GABA receptors

2-Baclofen: synthetic GABA derivatives

3-Tizandine: central α2 agonist.

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Peripheral muscle relaxant

- ♣ **Drugs that decrease synthesis of ACh**

Hemicholinium: decrease neuronal uptake of choline

- ♣ **Drugs that decrease release of ACh**

Local anesthetic

Botulinum toxin

- **Neuromuscular blockers**

Direct acting M relaxant

Dantrolene: it inhibit muscle contraction by preventing release of calcium from sarcoplasmic reticulum .act as antagonize to ryanodine receptors .

Clinical uses of muscle relaxant:

1- General anesthesia

2- Chemical restraint for wild animal

3- Strychnine poisoning

4- Muscle disorder