Cholinesterase inhibitors

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Mechanism of action

- Cholinesterase is an enzyme that cleaves acetylcholine to acetate and choline to end its action. It’s located in both pre and postsynapse.

- Cholinesterase inhibitors inactivate acetylcholinesterase by reversibly binding to the enzyme.

- Cholinesterase inhibitors indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine.

- Clearance is due to both hepatic metabolism (25–50%) and renal excretion (50–75%).
Effect on different organ systems:

**Cardiovascular receptors** — The predominant muscarinic effect on the heart is bradycardia that can progress to sinus arrest.

**Pulmonary receptors** — Muscarinic stimulation can result in bronchospasm (smooth muscle contraction) and increased respiratory tract secretions.

**Gastrointestinal receptors** — Muscarinic stimulation increases peristaltic activity (esophageal, gastric, and intestinal) and glandular secretions (e.g., salivary). Postoperative nausea, vomiting, and fecal incontinence have been attributed to the use of cholinesterase inhibitors.

**Eye** — Miosis
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Muscarinic Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Decreased heart rate, bradyarrhythmias</td>
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<tr>
<td>Pulmonary</td>
<td>Bronchospasm, bronchial secretions</td>
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<tr>
<td>Cerebral</td>
<td>Diffuse excitation¹</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Intestinal spasm, increased salivation</td>
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<tr>
<td>Genitourinary</td>
<td>Increased bladder tone</td>
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<tr>
<td>Ophthalmological</td>
<td>Pupillary constriction</td>
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</tbody>
</table>
Classified to:

- Reversible: **Neostigmine**, physostigmine, pyridostigmine, Endrophnium
- Irreversible: Isoflurophate, Echothiphate
Specific Cholinesterase Inhibitors

NEOSTIGMINE

• Polar/lipid insoluble: doesn’t enter the CNS
• Dosage & Packaging : The **maximum** recommended dose of neostigmine is **0.08 mg/kg** (up to 5 mg in adults), but smaller amounts often suffice and larger doses have also been given safely.
• Some clinicians use a dose of **0.04 mg/kg** (or 2.5 mg) if the preexisting blockade is **mild to moderate** and a dose of **0.08 mg/kg** (or 5 mg) if **intense** paralysis is being reversed; other clinicians use the “full dose” for all patients.
• The effects of neostigmine (0.04 mg/kg) are usually **apparent** in 5 min, **peak** at 10 min, and **last more than 1 h.**
Clinical uses

• **Primary action?** at the end of operation available to compete with the nondepolarizing agent, thereby reestablishing normal neuromuscular transmission

  **Note:** any prolongation of action of a nondepolarizing muscle relaxant from renal or hepatic insufficiency will probably be accompanied by a corresponding increase in the duration of action of a cholinesterase inhibitor.

• It can be used for urinary retention resulting from general anesthesia

• In the treatment of myasthenia gravis
Side Effects

- Salivation
- Bradycardia, decrease blood pressure
- abdominal pain, nausea
- bronchospasm
- urinary urgency
- Meiosis
- Sweaty skin
Role of neostigmine in anesthesia

- Generally: side effects of cholinesterase inhibitors are minimized by prior or concomitant administration of an anticholinergic agent.

- Neostigmine increase amount of Ach so Ach competes with non depolarizing drugs and decrease their effect but leads to many side effects resulting from increased Ach concentration and activation of parasympathetic system leading to bradycardia, meiosis, hyper-salivation, intestinal hypermotility so we combine atropine with neostigmine in one syringe to counteract the side effects.
• **Pyridostigmine**; slower onset and less potent
• **Edrophonium**: less potent but the most rapid onset of action and shortest duration.
• **Physostigmine**; lipid soluble so can cross BBB (the only one)
Thank you