Lecture Notes for Session 5: Indirect-Acting Agents - Reversible Cholinesterase Inhibitors

SNS College of Pharmacy and Health Sciences

Medicinal Chemistry - Unit III: Cholinergic Neurotransmitters

Prepared by: Faculty of Medicinal Chemistry

Date: June 26, 2025

1 Indirect-Acting Agents: Reversible Cholinesterase Inhibitors

1.1 Overview

Indirect-acting parasympathomimetic agents enhance cholinergic activity by inhibiting acetylcholinesterase (AChE), the enzyme responsible for hydrolyzing acetylcholine (ACh) in the synaptic cleft. This session focuses on reversible cholinesterase inhibitors: Physostigmine, Neostigmine, Pyridostigmine, Edrophonium chloride, Tacrine hydrochloride, and Ambenonium chloride. These agents increase ACh levels, amplifying muscarinic and nicotinic receptor activation, and are used in various clinical conditions.

1.2 Learning Objectives

- Understand the mechanism of reversible cholinesterase inhibitors.
- Identify the chemical structures and Structure-Activity Relationships (SAR) of Physostigmine, Neostigmine, Pyridostigmine, Edrophonium chloride, Tacrine hydrochloride, and Ambenonium chloride.
- Describe their pharmacokinetics and clinical applications.
- Evaluate the therapeutic benefits and limitations of these agents.

2 Mechanism of Reversible Cholinesterase Inhibition

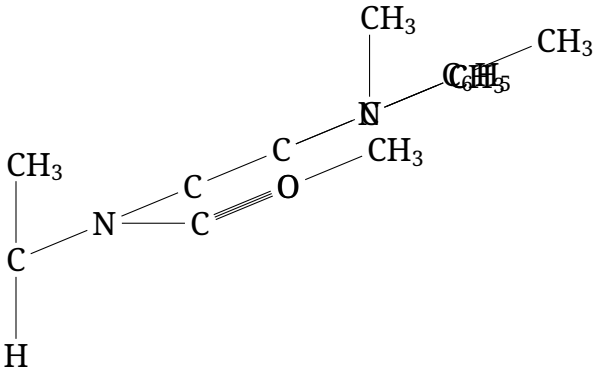
- **General Mechanism**: Reversible inhibitors bind to the active site of AChE, temporarily preventing ACh hydrolysis. This increases ACh concentration in the synaptic cleft, enhancing cholinergic signaling.
- **Binding Types**:
  - Carbamates (e.g., Physostigmine, Neostigmine): Form a carbamoylated enzyme intermediate, slowly hydrolyzed (pseudo-reversible).
  - Competitive inhibitors (e.g., Edrophonium): Bind reversibly to the anionic site via ionic and hydrogen bonds.
  - Non-carbamates (e.g., Tacrine): Bind to the peripheral anionic site or catalytic site, reversible via dissociation.
- **Reaction**:

$$ACh + H_2O -> [AChE]Choline + Acetate$$

  Inhibitor binds to AChE, preventing this reaction, thus increasing ACh levels.

3 Physostigmine

3.1 Chemical Structure



- Natural alkaloid from the Calabar bean.
- Carbamate group for AChE inhibition; tertiary amine enhances CNS penetration.

3.2 Mechanism of Action

- Carbamoylates the serine residue in AChE's active site, forming a stable but reversible complex.
- Increases ACh at muscarinic and nicotinic synapses.

3.3 Pharmacokinetics

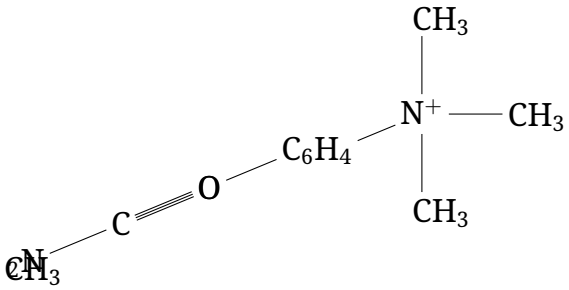
- Administered topically (ophthalmic solution) or parenterally; limited oral bioavailability.
- Crosses blood-brain barrier due to tertiary amine, affecting CNS.
- Duration: 2–4 hours.

3.4 Clinical Applications

- Glaucoma: Reduces intraocular pressure by enhancing aqueous humor outflow.
- Atropine poisoning: Reverses anticholinergic effects in the CNS and PNS.
- Alzheimer's disease (historical): Enhances cognitive function (largely replaced by newer agents).

4 Neostigmine

4.1 Chemical Structure



- Synthetic carbamate with a quaternary ammonium group, limiting CNS penetration.

4.2 Mechanism of Action

- Carbamoylates AChE, prolonging ACh action at muscarinic and nicotinic receptors.
- Primarily peripheral effects due to poor CNS penetration.

4.3 Pharmacokinetics

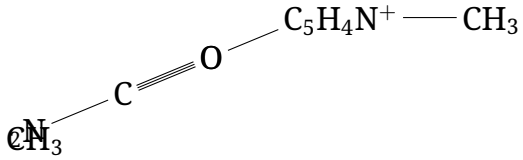
- Administered orally, parenterally, or topically (ophthalmic).
- Duration: 2–4 hours.
- Poor CNS penetration due to quaternary ammonium structure.

4.4 Clinical Applications

- Myasthenia gravis: Enhances neuromuscular transmission by increasing ACh at nicotinic receptors.
- Postoperative ileus and urinary retention: Stimulates gastrointestinal and bladder motility.
- Reversal of non-depolarizing neuromuscular blockers in anesthesia.

5 Pyridostigmine

5.1 Chemical Structure



- Quaternary ammonium with a pyridine ring, structurally similar to Neostigmine.

5.2 Mechanism of Action

- Carbamoylates AChE, similar to Neostigmine, with primarily peripheral effects.
- Enhances muscarinic and nicotinic receptor activation.

5.3 Pharmacokinetics

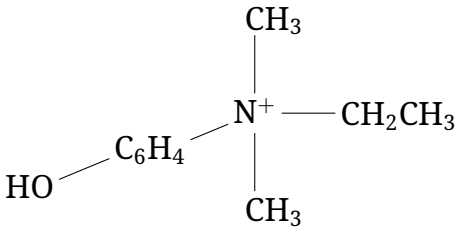
- Administered orally or parenterally.
- Longer duration than Neostigmine (4–6 hours).
- Poor CNS penetration.

5.4 Clinical Applications

- Myasthenia gravis: Preferred for long-term management due to longer duration.
- Pretreatment for nerve gas exposure: Enhances ACh levels to counteract organophosphate poisoning.

6 Edrophonium Chloride

6.1 Chemical Structure



- Quaternary ammonium with a phenolic group, no carbamate.

6.2 Mechanism of Action

- Competitively binds to AChE's anionic site via ionic and hydrogen bonds.
- Short-acting, reversible inhibition due to rapid dissociation.

6.3 Pharmacokinetics

- Administered intravenously.
- Very short duration: 5–10 minutes.
- Peripheral action only.

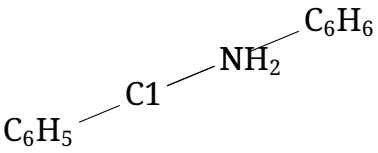
6.4 Clinical Applications

- Diagnosis of myasthenia gravis: Short duration used in Tensilon test to assess muscle strength improvement.

- Reversal of non-depolarizing neuromuscular blockers.

7 Tacrine Hydrochloride

7.1 Chemical Structure



- Acridine derivative with a primary amine, no quaternary ammonium.

7.2 Mechanism of Action

- Non-competitive, reversible inhibition of AChE by binding to the peripheral anionic site.
- Enhances ACh in the CNS, with minimal peripheral effects.

7.3 Pharmacokinetics

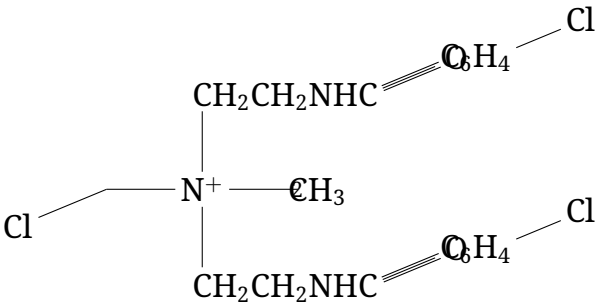
- Administered orally.
- Crosses blood-brain barrier, significant CNS effects.
- Duration: 6–8 hours.
- Metabolized by CYP1A2; risk of hepatotoxicity.

7.4 Clinical Applications

- Alzheimer's disease (historical): Enhances cognitive function by increasing CNS ACh levels.
- Largely replaced by safer agents (e.g., donepezil) due to hepatotoxicity.

8 Ambenonium Chloride

8.1 Chemical Structure



- Bis-quaternary ammonium with amide groups, high potency.

8.2 Mechanism of Action

- Reversible inhibition of AChE via binding to the active site.
- Enhances ACh at peripheral muscarinic and nicotinic receptors.

8.3 Pharmacokinetics

- Administered orally.
- Duration: 4–8 hours.
- Poor CNS penetration due to bis-quaternary structure.

8.4 Clinical Applications

- Myasthenia gravis: Enhances neuromuscular transmission.
- Less commonly used due to availability of Neostigmine and Pyridostigmine.

9 Structure-Activity Relationship (SAR)

- **Carbamates (Physostigmine, Neostigmine, Pyridostigmine)**:
  - Carbamate group forms a covalent bond with AChE's serine, slowly hydrolyzed.
  - Quaternary ammonium enhances peripheral selectivity; tertiary amine (Physostigmine) allows CNS penetration.
- **Non-Carbamates (Edrophonium, Tacrine)**:
  - Bind via ionic/hydrogen bonds or hydrophobic interactions, fully reversible.
  - Lack of quaternary ammonium (Tacrine) enables CNS activity.
- **Bis-Quaternary (Ambenonium)**: Enhanced potency due to dual binding to AChE's anionic sites.

10 Comparison of Reversible Cholinesterase Inhibitors

Agent	Structure	Mechanism	Clinical Use
Physostigmine	Carbamate, tertiary amine	Carbamoylation, CNS	Glaucoma, atro
Neostigmine	Carbamate, quaternary	Carbamoylation, peripheral	Myasthenia gra
Pyridostigmine	Carbamate, quaternary	Carbamoylation, peripheral	Myasthenia gra
Edrophonium	Quaternary, no carbamate	Competitive, peripheral	Diagnosis of m
Tacrine	Acridine, no quaternary	Non-competitive, CNS	Alzheimer's (hi
Ambenonium	Bis-quaternary, amide	Reversible, peripheral	Myasthenia gra

Table 1: Comparison of Reversible Cholinesterase Inhibitors

11 Pharmacological and Clinical Considerations

- **Therapeutic Benefits**: Enhance ACh for conditions like myasthenia gravis, glaucoma, and Alzheimer's disease.
- **Side Effects**: Cholinergic excess (e.g., salivation, bradycardia, bronchoconstriction). Managed by dose adjustment or atropine.
- **Limitations**: Tacrine's hepatotoxicity; Edrophonium's short duration limits therapeutic use.

12 Summary

- Reversible cholinesterase inhibitors (Physostigmine, Neostigmine, Pyridostigmine, Edrophonium, Tacrine, Ambenonium) increase ACh levels by inhibiting AChE.
- Structural features (carbamate, quaternary ammonium) determine potency, duration, and CNS penetration.
- Clinical applications include myasthenia gravis, glaucoma, Alzheimer's, and reversal of neuromuscular blockers.

13 References

- Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 12th Edition.
- Foye's Principles of Medicinal Chemistry, 7th Edition.
- PubChem (`https://pubchem.ncbi.nlm.nih.gov`): Chemical structures of cholinesterase inhibitors.
- DrugBank (`https://go.drugbank.com`): Pharmacological data on cholinergic drugs.