Lecture Notes for Session 10: Synthetic Cholinergic Blocking Agents - Part 2

SNS College of Pharmacy and Health Sciences

Medicinal Chemistry - Unit III: Cholinergic Neurotransmitters

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1 Synthetic Cholinergic Blocking Agents - Part 2

1.1 Overview

Synthetic cholinergic blocking agents, or anticholinergic agents, competitively inhibit acetylcholine (ACh) binding to muscarinic receptors, reducing parasympathetic effects such as smooth muscle contraction, glandular secretion, and bradycardia. This session covers nine synthetic agents: Methantheline bromide, Propantheline bromide, Benztropine mesylate, Orphenadrine citrate, Biperidine hydrochloride, Procyclidine hydrochloride, Tridihexethyl chloride, Isopropamide iodide, and Ethopropazine hydrochloride, focusing on their chemical structures, mechanisms, pharmacokinetics, and clinical applications.

1.2 Learning Objectives

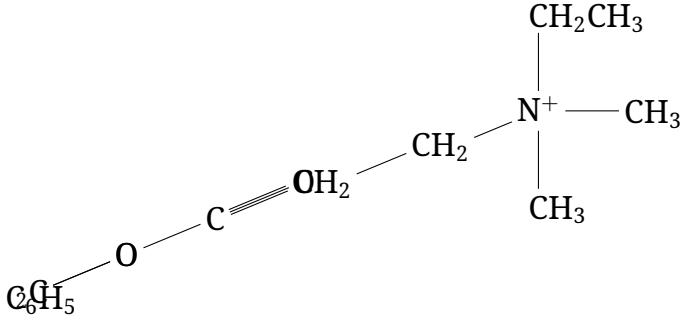
- Understand the mechanism of action of synthetic cholinergic blocking agents.
- Describe the chemical structures and Structure-Activity Relationships (SAR) of the listed agents.
- Explain their pharmacokinetics and therapeutic uses, particularly in gastrointestinal and neurological disorders.
- Evaluate their advantages, side effects, and clinical significance.

2 Introduction to Synthetic Cholinergic Blocking Agents

- **Definition**: Synthetic anticholinergic agents are designed to block muscarinic receptors (M1–M5), offering improved selectivity and reduced side effects compared to natural alkaloids like atropine.
- **Mechanism**: Competitively antagonize ACh at muscarinic receptors, inhibiting parasympathetic responses.
- **Clinical Applications**: Used in gastrointestinal disorders (e.g., peptic ulcer, IBS), neurological conditions (e.g., Parkinson's disease), and other applications requiring reduced cholinergic activity.

3 Methantheline Bromide

3.1 Chemical Structure



- Quaternary ammonium with an ester group and xanthene moiety.

3.2 Mechanism of Action

- Muscarinic antagonist, targeting M3 receptors in the gastrointestinal tract.
- Reduces gastric acid secretion and smooth muscle motility.

3.3 Pharmacokinetics

- Administered orally.
- Poor CNS penetration due to quaternary ammonium structure.
- Duration: 6–8 hours.
- Limited systemic absorption.

3.4 Clinical Applications

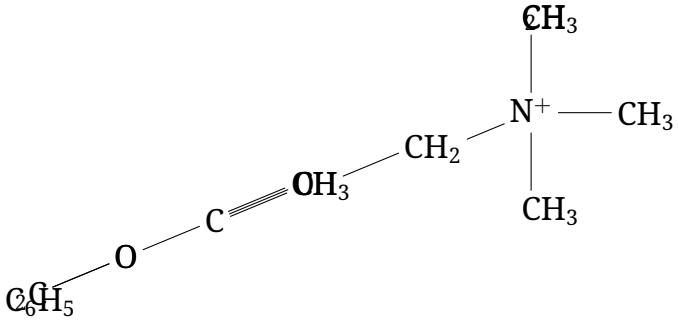
- Peptic ulcer (historical): Reduces gastric acid secretion.
- Gastrointestinal spasms: Relieves motility in IBS.

3.5 Side Effects

- Dry mouth, constipation, blurred vision.
- Minimal CNS effects due to peripheral action.

4 Propantheline Bromide

4.1 Chemical Structure



- Quaternary ammonium with an ester group and isopropyl substituents.

4.2 Mechanism of Action

- Muscarinic antagonist, primarily M3 receptors in the gastrointestinal tract.
- Inhibits gastric motility and acid secretion.

4.3 Pharmacokinetics

- Administered orally.
- No CNS penetration; duration: 6–8 hours.
- Poor oral bioavailability due to quaternary structure.

4.4 Clinical Applications

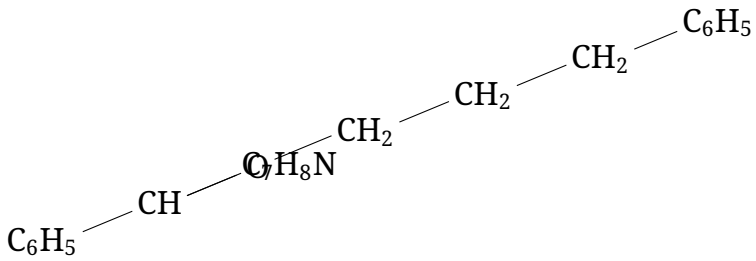
- Peptic ulcer: Reduces gastric acid secretion.
- IBS: Relieves abdominal cramping and spasms.

4.5 Side Effects

- Dry mouth, constipation, urinary retention.
- Minimal systemic effects.

5 Benztropine Mesylate

5.1 Chemical Structure



- Tertiary amine with a tropane-like structure, similar to atropine.

5.2 Mechanism of Action

- Muscarinic antagonist (M1 receptors) with significant CNS effects.
- Restores dopamine-ACh balance in Parkinson's disease.

5.3 Pharmacokinetics

- Administered orally or intramuscularly.
- Crosses blood-brain barrier; duration: 6–48 hours.
- Slow onset, long-acting.

5.4 Clinical Applications

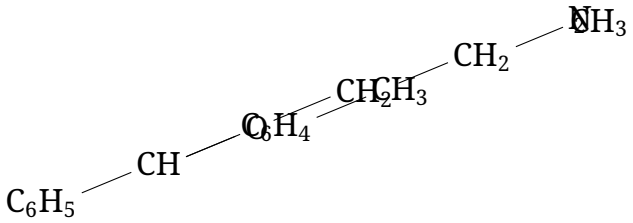
- Parkinson's disease: Reduces tremors and rigidity.
- Extrapyramidal symptoms (EPS): Manages drug-induced parkinsonism (e.g., antipsychotics).

5.5 Side Effects

- Dry mouth, constipation, confusion, memory impairment.
- CNS effects prominent in elderly.

6 Orphenadrine Citrate

6.1 Chemical Structure



- Tertiary amine with an ether linkage and diphenylmethane structure.

6.2 Mechanism of Action

- Muscarinic antagonist with antihistaminic and muscle relaxant properties.
- CNS and peripheral effects, primarily for muscle spasticity.

6.3 Pharmacokinetics

- Administered orally or intramuscularly.
- CNS penetration; duration: 4–6 hours.
- Metabolized in liver; good bioavailability.

6.4 Clinical Applications

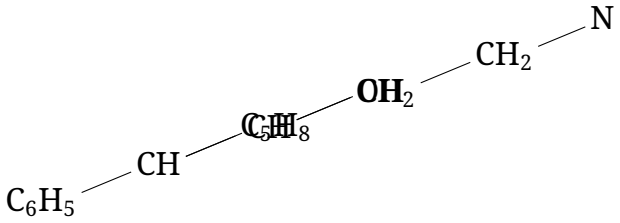
- Muscle spasms: Relieves skeletal muscle spasticity (e.g., in musculoskeletal injuries).
- Parkinson's disease (adjunct): Reduces tremors.

6.5 Side Effects

- Drowsiness, dry mouth, dizziness.
- CNS effects: Confusion, hallucinations (less than benztropine).

7 Biperidine Hydrochloride

7.1 Chemical Structure



- Tertiary amine with a piperidine ring and hydroxyl group.

7.2 Mechanism of Action

- Muscarinic antagonist, primarily M1 receptors in the CNS.
- Balances cholinergic-dopaminergic activity in Parkinson's disease.

7.3 Pharmacokinetics

- Administered orally or parenterally.
- Crosses blood-brain barrier; duration: 6–8 hours.

7.4 Clinical Applications

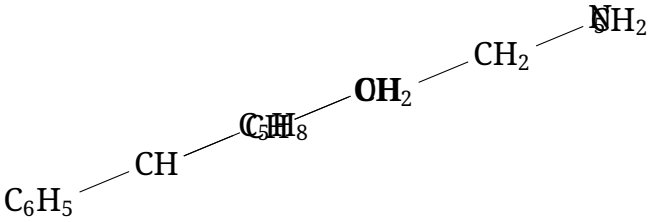
- Parkinson's disease: Reduces tremors and rigidity.
- Drug-induced EPS: Manages parkinsonism from antipsychotics.

7.5 Side Effects

- Dry mouth, constipation, sedation, cognitive impairment.

8 Procyclidine Hydrochloride

8.1 Chemical Structure



- Tertiary amine with a pyrrolidine ring and hydroxyl group.

8.2 Mechanism of Action

- Muscarinic antagonist, targeting M1 receptors in the CNS.
- Reduces cholinergic overactivity in Parkinson's disease.

8.3 Pharmacokinetics

- Administered orally.
- CNS penetration; duration: 4–6 hours.
- Moderate bioavailability.

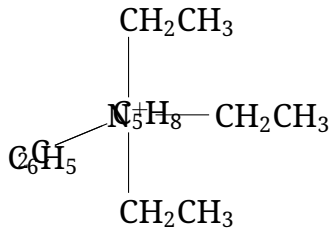
Clinical Applications

- Parkinson's disease: Reduces tremors and muscle rigidity.
- EPS: Treats antipsychotic-induced parkinsonism.

Side Effects

- Dry mouth, blurred vision, sedation, confusion.

Tridihexethyl Chloride Chemical Structure



- Quaternary ammonium with a cyclohexyl ring.

Mechanism of Action

- Muscarinic antagonist, targeting M3 receptors in the gastrointestinal tract.
- Reduces gastric motility and secretions.

Pharmacokinetics

- Administered orally.
- No CNS penetration; duration: 6–8 hours.
- Poor systemic absorption.

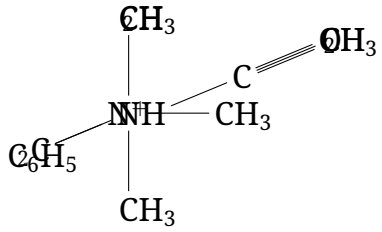
Clinical Applications

- Peptic ulcer: Reduces gastric acid secretion.
- IBS: Relieves gastrointestinal spasms.

Side Effects

- Dry mouth, constipation, urinary retention.
- Minimal CNS effects.

Isopropamide Iodide Chemical Structure



- Quaternary ammonium with an amide group.

Mechanism of Action

- Muscarinic antagonist, primarily M3 receptors in the gastrointestinal tract.
- Inhibits gastric motility and acid secretion.

Pharmacokinetics

- Administered orally.
- No CNS penetration; duration: 8–12 hours.
- Long-acting due to quaternary structure.

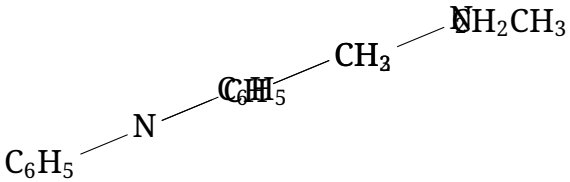
Clinical Applications

- Peptic ulcer: Reduces gastric acid secretion.
- IBS: Relieves abdominal cramping.

Side Effects

- Dry mouth, constipation, blurred vision.

Ethopropazine Hydrochloride Chemical Structure



- Tertiary amine with a phenothiazine structure.

Mechanism of Action

- Muscarinic antagonist with M1 receptor selectivity in the CNS.
- Also exhibits antihistaminic and antidopaminergic effects.

Pharmacokinetics

- Administered orally.
- CNS penetration; duration: 4–6 hours.
- Metabolized in liver.

Clinical Applications

- Parkinson's disease: Reduces tremors.
- Drug-induced EPS: Manages parkinsonism.

Side Effects

- Sedation, dry mouth, orthostatic hypotension.
- CNS effects due to phenothiazine structure.

Structure-Activity Relationship (SAR)

- **Amine Group**: Tertiary amines (Benztropine, Orphenadrine, Biperidine, Procyclidine, Ethopropazine) allow CNS penetration; quaternary ammoniums (Methantheline, Propantheline, Tridihexethyl, Isopropamide) restrict to peripheral action.
- **Ester/Amide/Ether**: Ester (Methantheline, Propantheline) or ether (Orphenadrine) groups enhance receptor binding; amide (Isopropamide) reduces potency but increases stability.
- **Bulky Groups**: Aromatic (Benztropine, Ethopropazine) or cycloalkyl (Tridihexethyl, Procyclidine) groups enhance antagonism.
- **Ring Systems**: Tropane-like (Benztropine), piperidine (Biperidine), or pyrrolidine (Procyclidine) increase M1 selectivity for CNS effects.

Comparison of Synthetic Cholinergic Blocking Agents

Agent	**Structure**	**Receptor**	**Clinical Use**	**Admin**
Methantheline	Quaternary, ester	M3 (GI)	Peptic ulcer, IBS	Oral
Propantheline	Quaternary, ester	M3 (GI)	Peptic ulcer, IBS	Oral
Benztropine	Tertiary, tropane	M1 (CNS)	Parkinson's, EPS	Oral, IM
Orphenadrine	Tertiary, ether	M1 (CNS)	Muscle spasms, Parkinson's	Oral, IM
Biperidine	Tertiary, piperidine	M1 (CNS)	Parkinson's, EPS	Oral, p
Procyclidine	Tertiary, pyrrolidine	M1 (CNS)	Parkinson's, EPS	Oral
Tridihexethyl	Quaternary, no ester	M3 (GI)	Peptic ulcer, IBS	Oral
Isopropamide	Quaternary, amide	M3 (GI)	Peptic ulcer, IBS	Oral
Ethopropazine	Tertiary, phenothiazine	M1 (CNS)	Parkinson's, EPS	Oral

Table 1: Comparison of Synthetic Cholinergic Blocking Agents

Pharmacological and Clinical Considerations

- **Therapeutic Benefits**: Effective for gastrointestinal disorders (Methantheline, Propantheline, Tridihexethyl, Isopropamide), Parkinson's disease, and EPS (Benztropine, Biperidine, Procyclidine, Ethopropazine), and muscle spasms (Orphenadrine).
- **Side Effects**: Anticholinergic effects (dry mouth, constipation, blurred vision); CNS effects (sedation, confusion) with tertiary amines.
- **Contraindications**: Glaucoma, urinary retention, bowel obstruction; caution in elderly for CNS effects.

Summary

- Synthetic cholinergic blocking agents (Methantheline, Propantheline, Benztropine, Orphenadrine, Biperidine, Procyclidine, Tridihexethyl, Isopropamide, Ethopropazine) are muscarinic antagonists with tailored structures for gastrointestinal or neurological applications.
- SAR emphasizes amine type, ester/amide/ether groups, and bulky moieties for receptor selectivity and CNS/peripheral action.
- Clinical uses include peptic ulcer, IBS, Parkinson's disease, EPS, and muscle spasms.

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 anticholinergic agents.
- DrugBank (`https://go.drugbank.com`): Pharmacological data on synthetic cholinolytics.