# Lecture Notes for Session 7: Cholinesterase Reactivator - Pralidoxime Chloride

*SNS College of Pharmacy and Health Sciences*

Medicinal Chemistry - Unit III: Cholinergic Neurotransmitters

Prepared by: Faculty of Medicinal Chemistry

Date: June 26, 2025

# 1 Cholinesterase Reactivator: Pralidoxime Chloride

## 1.1 Overview

Pralidoxime chloride (2-PAM) is a cholinesterase reactivator used primarily to treat organophosphate poisoning by restoring the activity of acetylcholinesterase (AChE), which is irreversibly inhibited by organophosphates. This session covers the chemical structure, mechanism of action, pharmacokinetics, clinical applications, and limitations of Pralidoxime chloride in the context of cholinergic pharmacology.

## 1.2 Learning Objectives

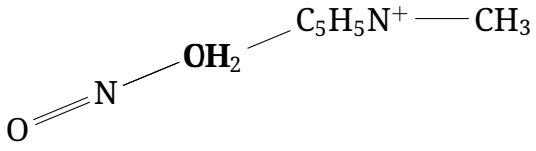
- Understand the role of Pralidoxime chloride as a cholinesterase reactivator.
- Describe its chemical structure and Structure-Activity Relationship (SAR).
- Explain the mechanism of action in reactivating AChE.
- Evaluate the clinical applications and limitations in treating organophosphate poisoning.

# 2 Introduction to Cholinesterase Reactivators

- **Purpose**: Cholinesterase reactivators reverse the inhibition of AChE caused by organophosphates (e.g., Isofluorphate, Parathion), which covalently phosphorylate the serine residue in AChE's active site, leading to acetylcholine (ACh) accumulation and cholinergic crisis.
- **Pralidoxime Chloride**: The primary reactivator used clinically, effective when administered before AChE "aging" occurs.
- **Clinical Context**: Used in organophosphate poisoning (e.g., pesticide exposure, nerve agents) to restore normal cholinergic signaling.

# 3 Pralidoxime Chloride

## 3.1 Chemical Structure




- Quaternary ammonium pyridine derivative with an oxime group (-CH=NOH).
- The oxime group is critical for nucleophilic attack on the phosphorylated AChE.
- Chloride salt enhances water solubility for intravenous administration.

### 3.2 Structure-Activity Relationship (SAR)

- **Oxime Group**: The nucleophilic -NOH group attacks the phosphorus atom in the phosphorylated AChE, displacing the phosphate and restoring enzyme activity.
- **Quaternary Ammonium**: Enhances binding to AChE's anionic site via ionic interactions, ensuring specificity and positioning the oxime for reactivation.
- **Pyridine Ring**: Provides structural stability and facilitates electron delocalization, enhancing the oxime's nucleophilicity.
- **Methyl Group**: Optimizes steric and electronic properties for effective binding.

## 4 Mechanism of Action

- **Organophosphate Inhibition**: Organophosphates (e.g., Parathion) phosphorylate the serine hydroxyl in AChE's active site, forming a stable covalent bond:

  $$AChE - Ser - OH + R_2P(=O) - X -> AChE - Ser - O - P(=O)(R_1)(R_2) + X$$

  This inhibits ACh hydrolysis, causing ACh accumulation.
- **Pralidoxime Reactivation**: The oxime group of Pralidoxime acts as a nucleophile, attacking the phosphorus atom, breaking the phosphate-serine bond, and restoring AChE activity:

  $$AChE - Ser - O - P(=O)(R_1)(R_2) + Pralidoxime -> AChE - Ser - OH + Phosphorylated$$

- **Time Sensitivity**: Effective only before "aging" (dealkylation of the phosphate group), which stabilizes the phosphorylated enzyme, making reactivation impossible.
- **Effects**: Restores AChE function, reducing excessive muscarinic (e.g., bronchoconstriction, salivation) and nicotinic (e.g., muscle paralysis) effects.

### 4.1 Pharmacological Effects

- Primarily reverses nicotinic symptoms (e.g., muscle weakness, fasciculations) at neuromuscular junctions.
- Limited effect on muscarinic symptoms, which are managed with atropine.
- Does not directly affect ACh levels or receptor activity but restores normal ACh hydrolysis.

## 5 Pharmacokinetics

- **Administration**: Intravenous (preferred for rapid action) or intramuscular in emergencies; oral administration is less common due to slower onset.

- **Distribution**: Limited CNS penetration due to quaternary ammonium structure; primarily acts in peripheral tissues.
- **Half-Life**: Approximately 1–2 hours.
- **Excretion**: Rapidly excreted unchanged in urine via renal tubular secretion.
- **Dosing**: Loading dose (e.g., 1–2 g IV over 15–30 minutes) followed by continuous infusion (e.g., 500 mg/h) in severe cases.

## 6 Clinical Applications

- **Organophosphate Poisoning**: Primary treatment for poisoning from pesticides (e.g., Parathion, Malathion) or nerve agents (e.g., sarin).
  - Used in combination with atropine to manage muscarinic symptoms.
  - Administered as soon as possible to prevent AChE aging.
- **n**erve gas Exposure: Military or emergency use to counteract chemical weapons.
- **Supportive Care**: Often combined with decontamination and ventilatory support.

## 7 Limitations and Considerations

- **Time-Dependent Efficacy**: Ineffective after AChE aging (hours to days, depending on the organophosphate).
- **CNS Penetration**: Poor blood-brain barrier crossing limits efficacy for CNS symptoms.
- **Side Effects**: Dizziness, blurred vision, hypertension, and tachycardia at high doses; generally well-tolerated.
- **Contraindications**: Avoid in carbamate poisoning (e.g., Physostigmine), as reactivation is unnecessary and may worsen symptoms.
- **Adjunct Therapy**: Must be used with atropine to control muscarinic effects; alone, it does not address all symptoms of poisoning.

## 8 Toxicological Context: Organophosphate Poisoning

- **Symptoms (DUMBBELSS)**: Diarrhea, Urination, Miosis, Bronchoconstriction, Bradycardia, Excitation (muscle), Lacrimation, Sweating, Salivation.
- **Nicotinic Effects**: Muscle fasciculations, weakness, paralysis.
- **CNS Effects**: Confusion, seizures, coma (less responsive to Pralidoxime due to poor CNS penetration).
- **Management Protocol**:

1. Administer atropine (2–6 mg IV, repeated as needed) to block muscarinic effects.
2. Administer Pralidoxime (1–2 g IV) within hours of exposure.
3. Provide supportive care (e.g., ventilation, decontamination).

## 9 Summary

- Pralidoxime chloride is a cholinesterase reactivator that restores AChE activity by dephosphorylating the enzyme in organophosphate poisoning.
- Its oxime group and quaternary ammonium structure enable specific and effective reactivation before enzyme aging.
- Primarily used in organophosphate poisoning, it is most effective when combined with atropine and administered early.
- Limitations include poor CNS penetration and time-dependent efficacy.

## 10 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 structure of Pralidoxime chloride.
- DrugBank (`https://go.drugbank.com`): Pharmacological data on Pralidoxime and organophosphates.