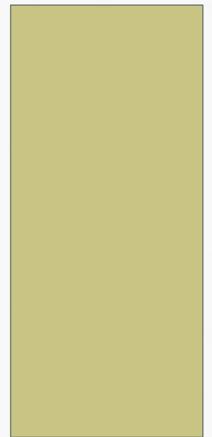


INSECTICIDES

BY DR. SWATHI SWAROOPA B
DEPARTMENT OF PHARMACY PRACTICE
J S S COLLEGE OF PHARMACY, OOTY

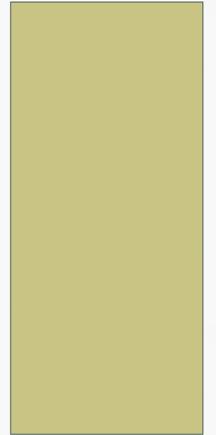


INSECTICIDES

These are compounds which kill or repel insects and related species.

- Organophosphates,
- Carbamates,
- Organochlorines,
- Pyrethrum and its derivatives (pyrethroids).

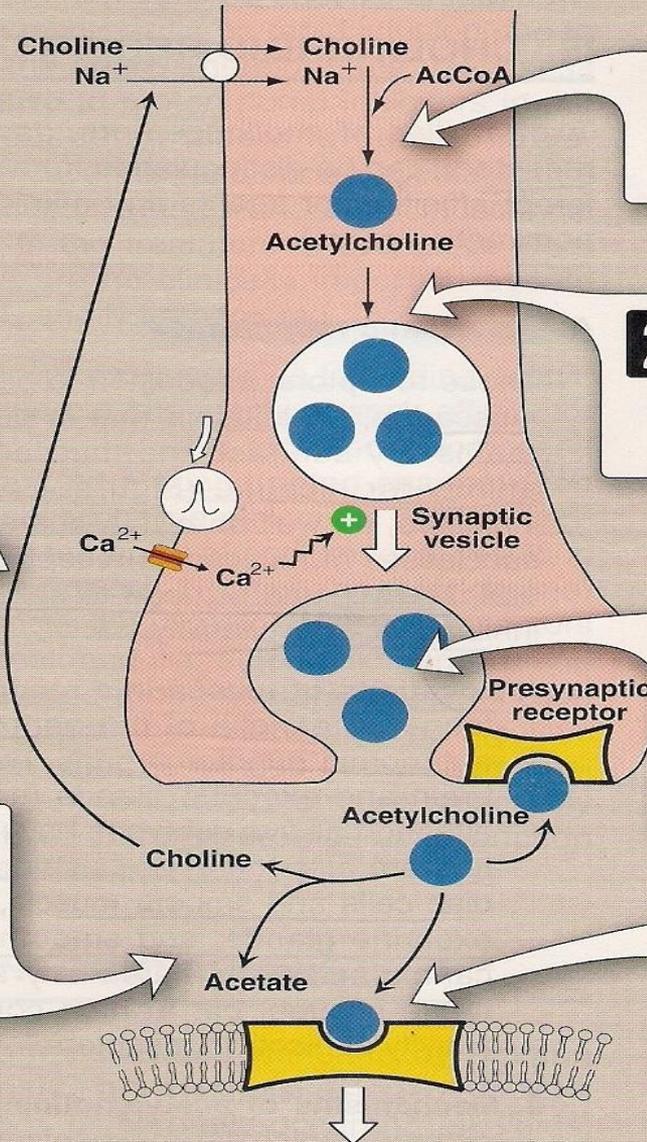
**ORGANOPHOSPHORUS COMPOUND &
ITS POISONING**



INTRODUCTION

- Organophosphorus compounds also known as cholinesterase inhibitors, and are widely used pesticides that may cause poisonings after accidental or suicidal exposure.
- AChE is an enzyme that degrades the neurotransmitter acetylcholine (ACh) into choline and acetic acid.
- Physical Appearance: Available as dusts, granules, or liquids
- Some products need to be diluted with water before use, and some are burnt to make smoke that kills insects

GENERAL MECHANISM OF AChE



1 SYNTHESIS OF ACETYLCHOLINE

- Transport of choline is inhibited by *hemicholinium*.

2 UPTAKE INTO STORAGE VESICLES

- Acetylcholine is protected from degradation in the vesicle.

3 RELEASE OF NEUROTRANSMITTER

- Release is blocked by botulinum toxin.
- Spider venom causes release of acetylcholine.

4 BINDING TO THE RECEPTOR

- Postsynaptic receptor is activated by binding of the neurotransmitter.

5 DEGRADATION OF ACETYLCHOLINE

- Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft.

6 RECYCLING OF CHOLINE

- Choline is taken up by the neuron.

INTRACELLULAR RESPONSE

MECHANISM OF ACTION OF ORGANOPHOSPHATE POISONING

Irreversibly bind to serine-OH group at the active site of acetylcholinesterase (AChE) → establish covalent bond (phosphorylation)



AGING: loss of alkyl group + strengthening of covalent bond



Phosphorylated AChE is very stable

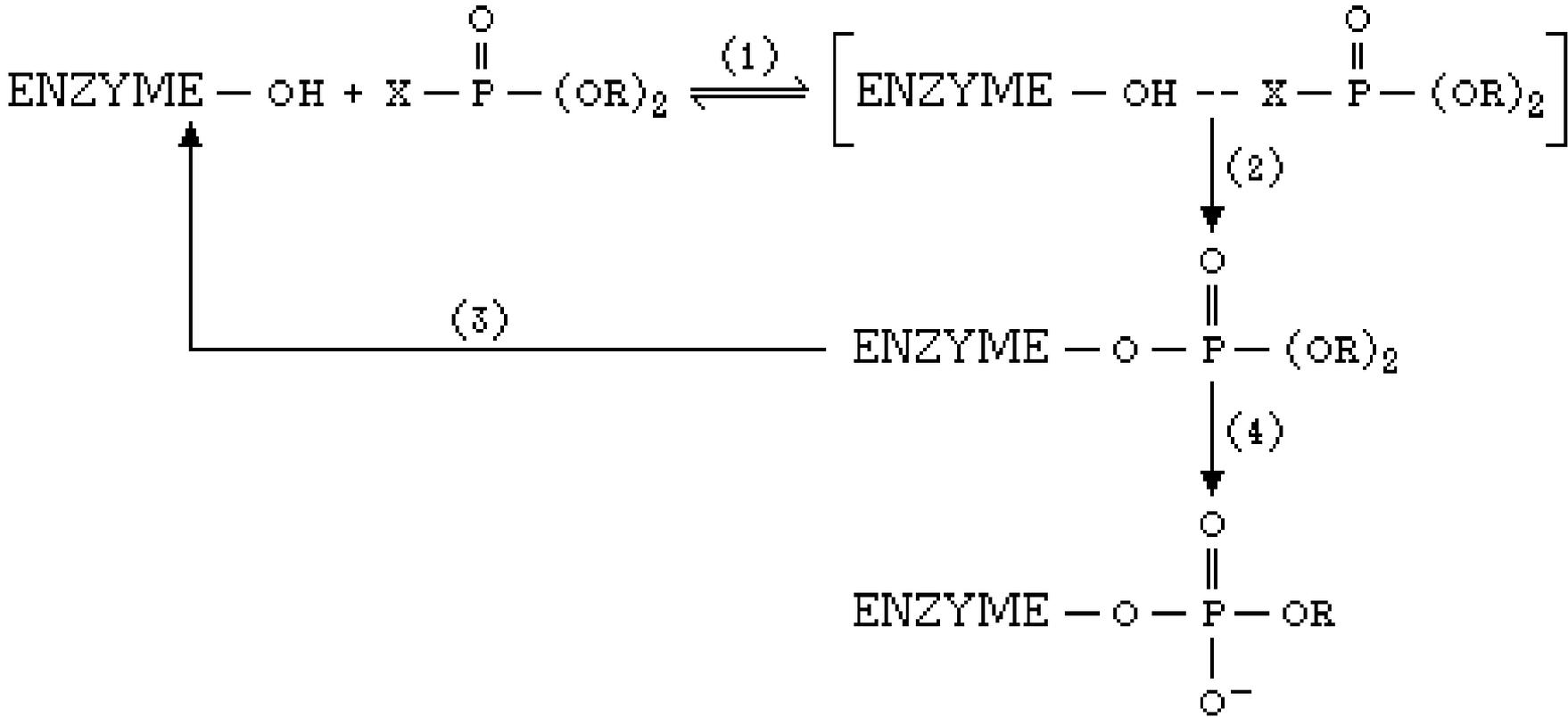


Inhibition of enzyme activity → accumulation of ACh in the synapse and NMJ



Overstimulation of cholinergic receptors

MECHANISM OF ACTION OF ORGANOPHOSPHORUS POISONING

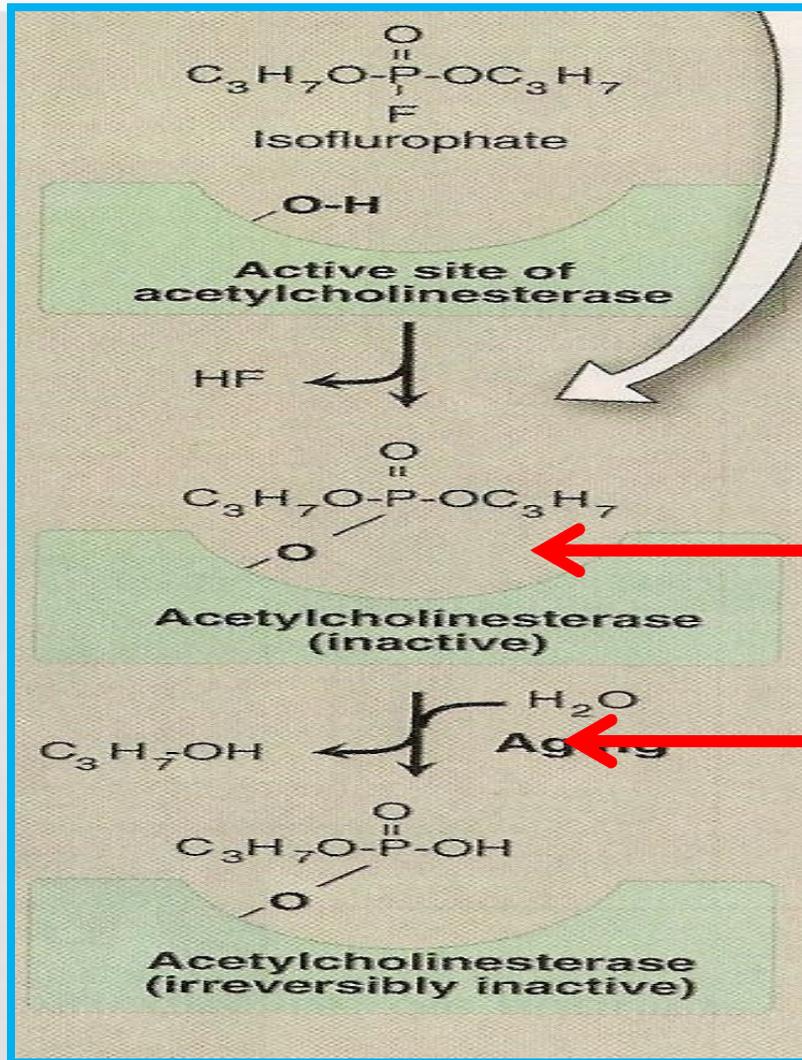


WHO 85199

Inhibition of an esterase enzyme by organophosphorus compounds.

- (1) Formation of Michaelis complex.
- (2) Phosphorylation of the enzyme.
- (3) Reactivation reaction.
- (4) "Aging".

MECHANISM OF ACTION OF ORGANOPHOSPHORUS POISONING



COVALENT BOND

AGING

MECHANISM OF ACTION

- ACh is found in the central and peripheral nervous system, neuromuscular junctions, and red blood cells (RBCs).
- Once AChE has been inactivated, ACh accumulates throughout the nervous system, resulting in **overstimulation of muscarinic and nicotinic receptors.**

MECHANISM OF ACTION

- Organophosphates exert powerful inhibitory action over other carboxylic ester hydrolases such as
 - Chymotrypsin,
 - Butyrylcholinesterase (pseudocholinesterase),
 - Plasma and hepatic carboxylesterases,
 - Paraoxonases, and other non-specific proteases
- Delayed peripheral neuropathy caused by organophosphates is due to phosphorylation of some esterase(s) other than acetylcholinesterase, such as neurotoxic esterase, also known as neuropathy target esterase (NTE).
- Neuropathy caused by inhibition of NTE may develop 2 to 5 weeks after an acute poisoning

LETHAL DOSE

**Extremely toxic (LD50:
1 to
50 mg/kg), or
Highly toxic (LD50: 51
to 500 mg/kg)—**

**Chlorfenvinphos,
Chlorpyrifos, Demeton,
Diazinon,
Dichlorvos, Dimethoate,
Disulfoton, Ediphenphos,
Ethion,
Fenitrothion, Fensulfothion,
Fenthion, Fonophos,
Formothion,
Methyl Parathion, Mevinphos,
Monocrotophos, Oxydemeton
Methyl, Phenthoate, Phorate,
Phosphamidon, Quinalphos,
TEPP, and Thiometon.**

LETHAL DOSE

Moderately toxic (LD50:
501 to 5000 mg/kg), or
slightly toxic (LD50:
more than 5000
mg/kg)

Abate, Acephate,
Coumaphos, Crufomate,
Famphur,
Glyphosate, Malathion,
Phenthoate, Primiphos
Methyl, Ronnel,
Temephos, Triazophos,
and Trichlorphon

TOXICOKINETICS OF OP

Absorbed by any route

- Transdermal,
 - Transconjunctival,
 - Inhalational,
 - Across the GI and GU mucosa, and
 - Through direct injection
-
- Manifestations usually begin within a few minutes to few hours.
 - May be delayed upto 12 hours or more in the case of certain compounds (e.g. fenthion, parathion).

ABSORPTION

Rate and Degree of absorption depends on

- Contact time with the skin
- lipophilicity of the agent
- Volatility of the pesticide
- Extent of coverage of the body surface
- Skin region affected

The onset and severity of symptoms depend on

1. The specific compound,
2. Amount,
3. Route of exposure, and
4. Rate of metabolic degradation.

DISTRIBUTION

- OP compounds accumulate rapidly in fat, liver, kidneys and salivary glands
- OP compounds generally are lipophilic and therefore cross the blood / brain barrier in most cases

BIOTRANSFORMATION

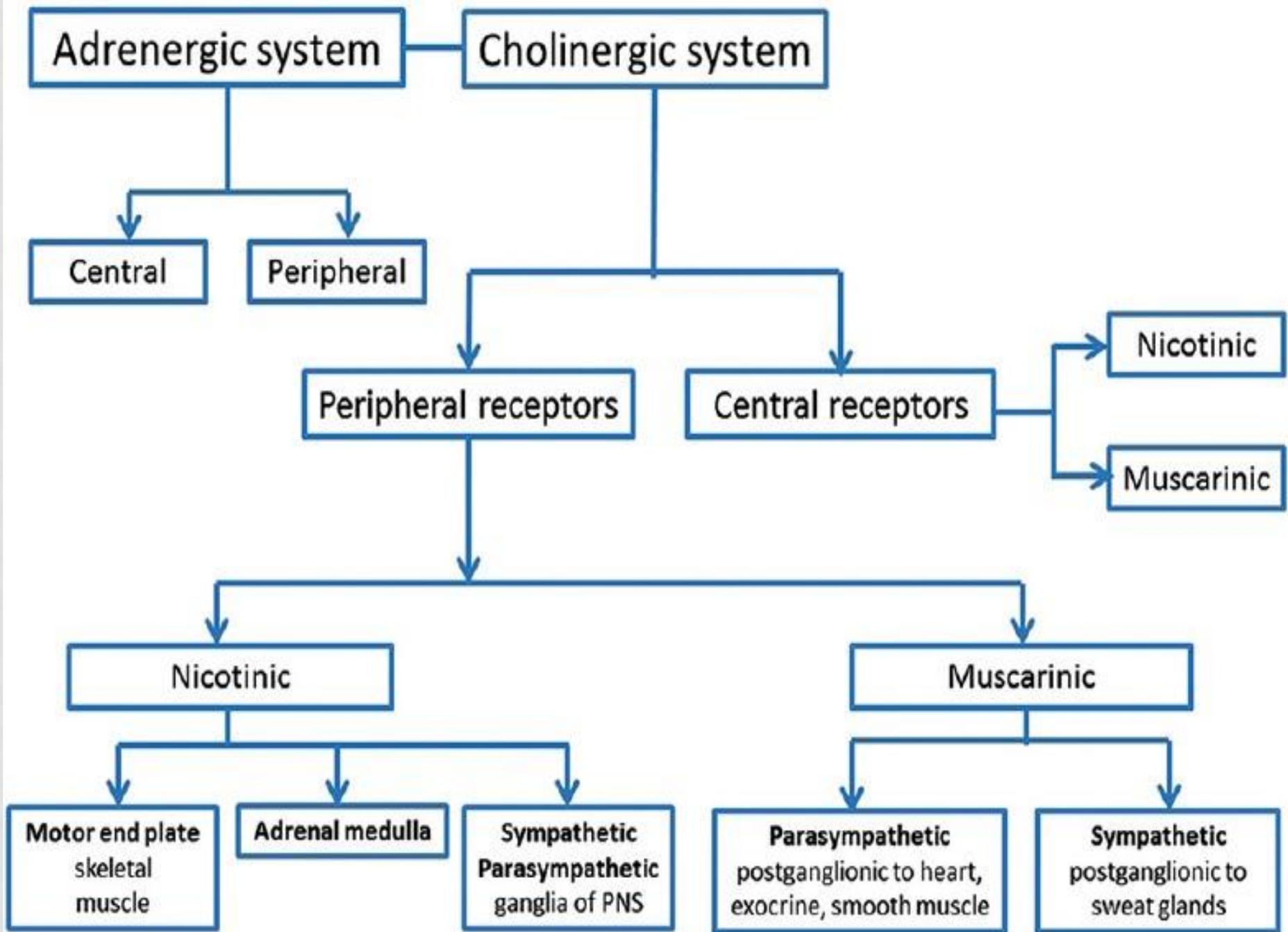
- OPs, after entering an organism, are metabolised with phase I and II enzymes
- Phase I of OP metabolism involves oxidation and hydrolysis:
 -
- Oxidation is the most important reaction in the activation of the OP thiono form to form active inhibitors of AcHE
- Hydrolysis of OPs takes place after oxidation, with the aid of the enzyme esterase A, also called paraoxonase. This reaction is important for OP detoxification processes.

- In phase II metabolism, detoxification reactions take place exclusively
- The most important enzymes involved in the metabolism of OPs are cytochromes CYP1A1, CYP3A4, CYP2B6 and CYP2C19.
- The first three have the highest affinity for desulphuration and activation to oxon.
- CYP2C19 is the most effective detoxicating enzyme

ELIMINATION

- Elimination of metabolites occurs mostly in urine with lesser amounts in faeces and expired air.

CLINICAL PRESENTATION



Adrenergic system

Cholinergic system

Central

Peripheral

Peripheral receptors

Central receptors

Nicotinic

Muscarinic

Nicotinic

Muscarinic

Motor end plate skeletal muscle

Adrenal medulla

Sympathetic Parasympathetic ganglia of PNS

Parasympathetic postganglionic to heart, exocrine, smooth muscle

Sympathetic postganglionic to sweat glands

ACUTE POISONING

- Acute cholinergic crisis
 - Muscarinic, Nicotinic, CNS effects
- Intermediate syndrome
- Organophosphate-induced delayed polyneuropathy (OPIDN)

| Type of receptor | Receptor sub-type | Action on | Manifestation |
|---------------------------------|-------------------|--|---|
| Nicotinic receptor stimulation | N1 (Nm) receptors | Neuromuscular junction | Weakness, fasciculations, cramps, paralysis |
| | N2 (Nn) receptors | Autonomic ganglia Adrenal medulla | Tachycardia, hypertension |
| Muscarinic receptor stimulation | M1-M5* | Central nervous system | Anxiety, restlessness, ataxia, convulsions, insomnia Dysarthria, tremors, coma, respiratory depression Circulatory collapse |
| | M2 receptor | Heart | Bradycardia, hypotension |
| | M3, M2 receptor* | Pupils | Blurred vision, miosis |
| | M3, M2 receptors* | Exocrine glands | Respiratory-rhinorrhea, bronchorrhea |
| | | | Gastrointestinal-increased salivation, diarrhea Ocular-increased lacrimation Others-excessive sweating |
| M3, M2 receptors* | Smooth muscles | Bronchospasm, abdominal pain, urinary incontinence | |

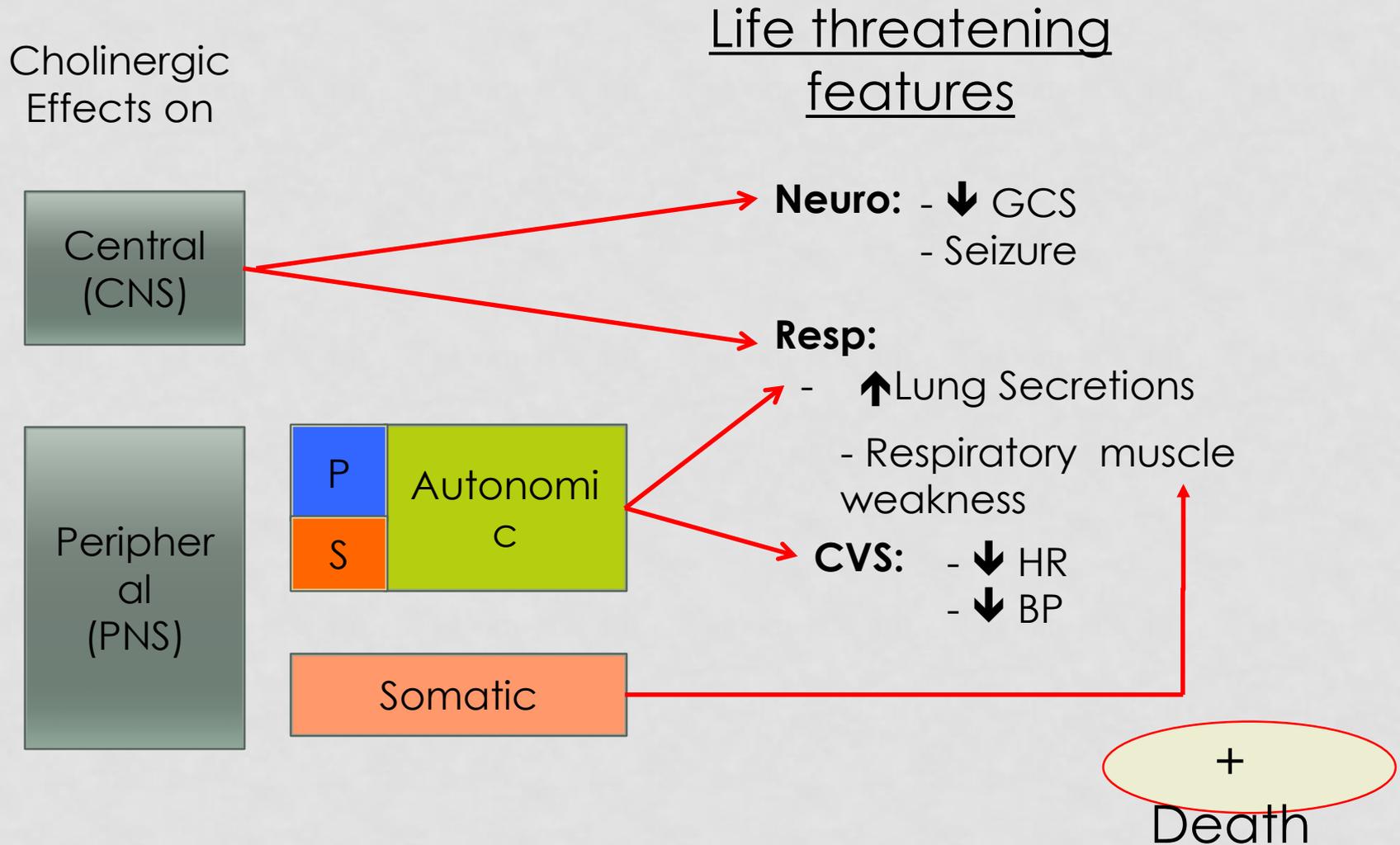
*M1 receptors play a critical role in cognitive function; M3 receptor effect predominates in the pupils, airway smooth muscles and mucus glands. Nicotinic receptors are sub-typed as N1 or Nm receptors and N2 or Nn receptors. Muscarinic receptors are sub-typed from M1 to M5

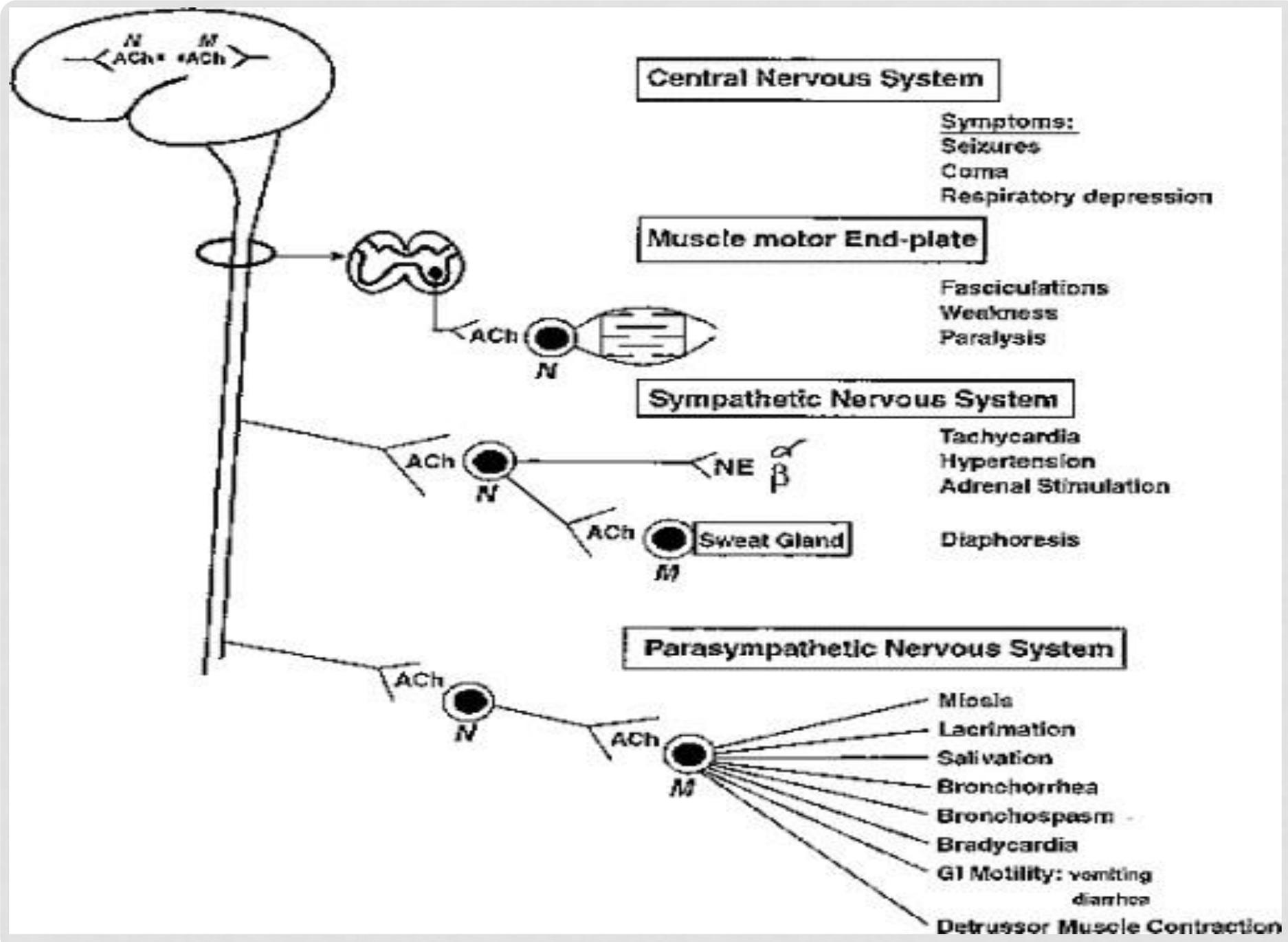
| Time of manifestation | Mechanism | Manifestation |
|------------------------------|--|---|
| Acute (minutes to 24-h) | Nicotinic receptor action Muscarinic receptor action | Weakness, fasciculations, cramps, paralysis Salivation, lacrimation, urination, defecation, gastric cramps, emesis, bradycardia, hypotension, miosis, bronchospasm |
| | Central receptors | Anxiety, restlessness, convulsions, respiratory depression |
| Delayed (24-h to 2-week) | Nicotinic receptor action Muscarinic receptor action Central receptors | Intermediate syndrome Cholinergic symptoms-bradycardia, miosis, salivation Coma, extra-pyramidal manifestations |
| Late (beyond 2-week) | Peripheral-neuropathy target esterase | Peripheral neuropathic process |

Summary of clinical features and antidotes in Acute Cholinergic Crisis

| | Muscarinic features | Nicotinic features | | CNS |
|--------------------|---|--|--|---|
| | Parasympathetic (Muscarinic receptor) | NMJ (NM receptor) | Symp Ganglia (NN receptor) | Muscarinic + ?NN receptor |
| Receptor Locations | Respiratory tract Gastrointestinal tract Cardiovascular system Exocrine glands Urinary bladder | Neuromuscular junction (NMJ) of striated muscles | Paravertebral sympathetic ganglia and Adrenal medulla | Various parts of the brain |
| Dangerous effects | Bronchospasm, Pulmonary oedema Diarrhoea, Vomiting, Abdominal cramps Bradycardia, Hypotension, Ventricular tachycardia Excessive secretions Urinary incontinence | Muscle weakness, Paralysis, Respiratory failure | Hypertension Tachycardia | Restlessness Seizures Coma Respiratory and circulatory depression |
| Antidote | Atropine Oximes | Oximes | ?Oximes | ?Atropine ? Diazepam |

OP POISONING – COMPLEX MULTI-SYSTEM PRESENTATION





Central Nervous System

- Symptoms:
 Seizures
 Coma
 Respiratory depression

Muscle motor End-plate

- Fasciculations
 Weakness
 Paralysis

Sympathetic Nervous System

- Tachycardia
 Hypertension
 Adrenal Stimulation

Parasympathetic Nervous System

- Miosis
- Lacrimation
- Salivation
- Bronchorrhea
- Bronchospasm
- Bradycardia
- GI Motility: vomiting
diarrhea
- Detrusor Muscle Contraction

CLINICAL MANIFESTATIONS OF OP POISONING

| Muscarinic | Nicotinic | Central |
|---|---|--|
| <p>Miosis Blurred vision Nausea Vomiting Diarrhoea Salivation Lacrimation Bradycardia Abdominal pain Diaphoresis Wheezing Urinary Incontinence Fecal Incontinence</p> | <p>Muscle Fasciculations Paralysis Pallor Muscle weakness Hypertension Tachycardia Mydriasis (rare)</p> | <p>Unconsciousness Confusion Toxic psychosis Seizures Fatigue Respiratory Depression Dysarthria Ataxia Anxiety</p> |

Various mnemonics have been used to describe the muscarinic signs of OP poisoning:

SLUDGE

- Salivation
- Lacrimation
- Urine incontinence
- Diarrhoea,
- Gastrointestinal cramps
- Emesis)

DUMBELS

- Diarrhoea
- Urination
- Miosis
- Bronchospasm, Bronc
horrhea
- Emesis
- Lacrimation
- Salivation

NICOTINIC: MATCH

M-Muscle weakness and fasciculation

A-Adrenal medulla activity ↑

T-Tachycardia

C-Cramping of skeletal muscle

H-Hypertension

ECG abnormalities-sinus bradycardia or tachycardia, atrioventricular and/or intraventricular conduction delays, ventricular tachycardia or fibrillations, torsades de pointes, prolongation of the PR, QRS, and/or QT intervals, ST-T wave changes, and atrial fibrillation

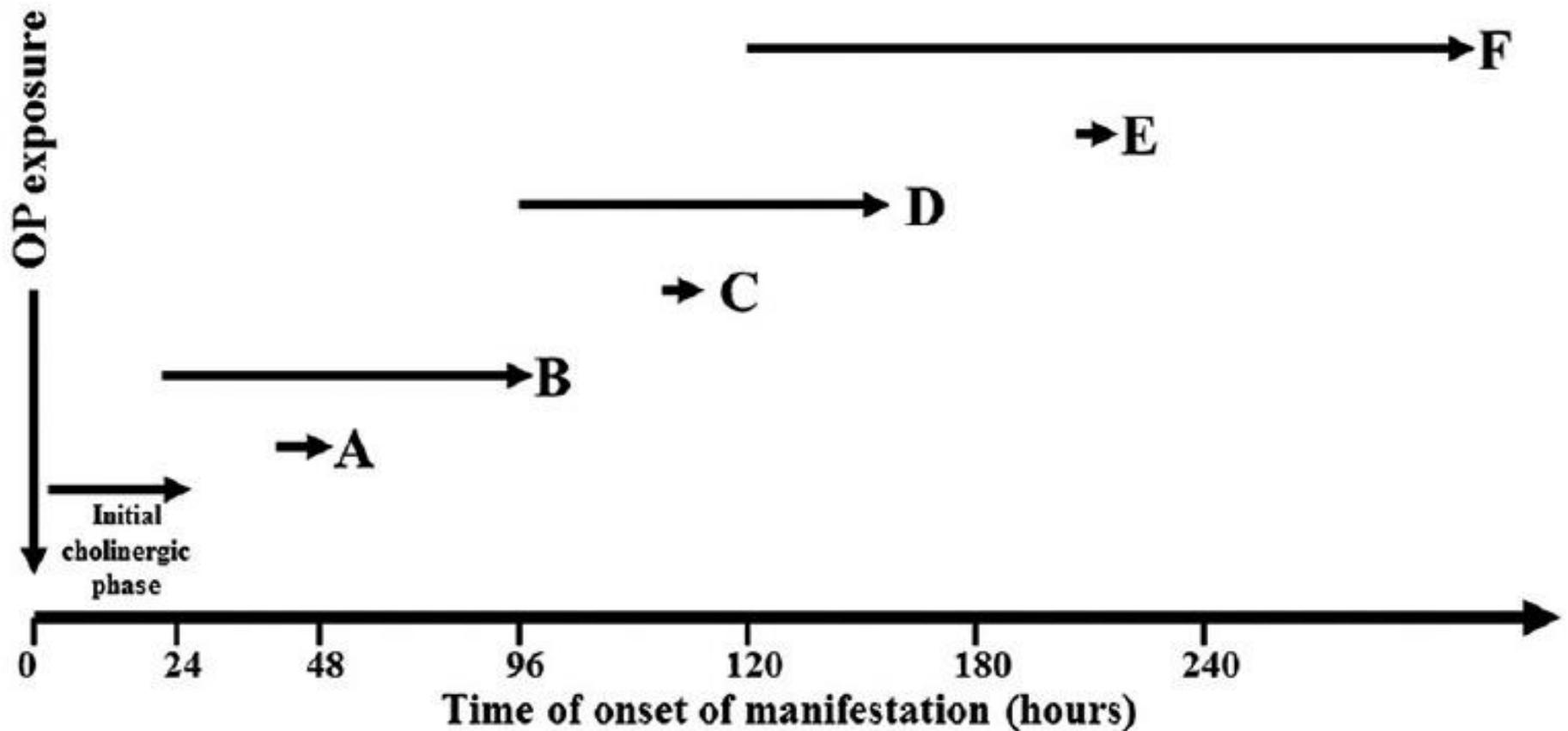
MUSCARINIC EFFECTS BY ORGAN SYSTEMS

- **Cardiovascular** - Bradycardia, hypotension
- **Respiratory** - Rhinorrhea, bronchorrhea, bronchospasm, cough, severe respiratory distress
- **Gastrointestinal** - Hypersalivation, nausea and vomiting, abdominal pain, diarrhea, fecal incontinence
- **Genitourinary** - Incontinence
- **Ocular** - Blurred vision, miosis
- **Glands** - Increased lacrimation, diaphoresis

Other symptoms

- Haemorrhagic pancreatitis
- Renal failure

Spectrum of delayed manifestations in organophosphate poisoning



- A - Delayed onset cholinergic phase (Davies et al, 1975) - 40 to 48 hours
- B - Intermediate Syndrome (Senanayake and Karalliedde, 1987) - 24 to 96 hours
- C - Late-onset intermediate syndrome (Yardan et al, 2007) - 114 hours
- D - Delayed onset encephalopathy or coma (Peter et al, 2008) - 4 to 6 days
- E - Cerebellar ataxia (Fonseka et al, 2003) - 8 days
- F - Delayed onset extra-pyramidal syndrome (Brahmi et al, 2004) - 5 to 15 days

INTERMEDIATE SYNDROME

- Occurs **1 to 4 days after poisoning** due to long-lasting cholinesterase inhibition and muscle necrosis

It may be due to **inadequate treatment of the acute episode**

- **Inadequate oxime** therapy,
- The **dose and route** of exposure,
- The **chemical structure** of the organophosphates,
- The **time to initiation** of therapy.

INTERMEDIATE SYNDROME

Muscle weakness and paralysis characterised by motor cranial nerve palsies, weakness of neck flexor and proximal limb muscles, and acute respiratory paresis. Paralytic signs include inability to lift the neck or sit up, ophthalmoparesis, slow eye movements, facial weakness, difficulty swallowing, limb weakness (primarily proximal), areflexia, respiratory paralysis, and death.

DELAYED SYNDROME

- Occurs **1 to 4 weeks** after poisoning due to **nerve demyelination**

Flaccid weakness and atrophy of distal limb muscles, or spasticity and Ataxia mixed sensory-motor neuropathy usually begins in the legs, causing burning or tingling, then weakness

Organophosphate-induced delayed polyneuropathy (OPIDN)

- This occurs about 1-3 weeks after acute exposure and an uncertain period following chronic exposure, due to degeneration of long myelinated nerve fibres.
 - Mechanism is inhibition of neuropathy target esterase (NTE) enzyme in nervous tissues by certain OP compounds (chloropyrifos)
 - A distinct acute or intermediate phase may not always precede its development
-

CHRONIC POISONING

- It usually occurs as an **occupational hazard in agriculturists**, especially those who are engaged in pesticide spraying of crops.
- Polyneuropathy
- CNS Effects
- Sheep Farmer's Disease: Psychiatric manifestations encountered in sheep farmers
- OPIDN

SEVERITY OF POISONING

- **Peradeniya Organophosphorous Poisoning (POP) Scale**
- **Severity based on AChE inhibition**

**PERADENIYA ORGANOPHOSPHOROUS
POISONING (POP) SCALE**

| | Clinical criteria | Score |
|------------------------|--------------------------------------|-------|
| Pupil size | > 2 mm | 0 |
| | < 2 mm | 1 |
| | Pin-point | 2 |
| Respiratory rate | < 20/min | 0 |
| | > 20/min | 1 |
| | > 20/min with central cyanosis | 2 |
| Heart rate | > 60/min | 0 |
| | 41–60/min | 1 |
| | < 40/min | 2 |
| Fasciculation | None | 0 |
| | Present, generalized or continuous | 1 |
| | Both, generalized and continuous | 2 |
| Level of consciousness | Conscious and rationale | 0 |
| | Impaired response to verbal commands | 1 |
| | No response to verbal commands | 2 |
| Seizures | Absent | 0 |
| | Present | 1 |

- A score of 0 to 3 is considered as **mild poisoning**,
- 4 to 7 as **moderate poisoning** and
- 8 to 11 as **severe poisoning**

SEVERITY BASED ON AChE INHIBITION

| Grade | Acetylcholinesterase activity (%) |
|----------|-----------------------------------|
| Mild | 50-90 |
| Moderate | 10-50 |
| Severe | <10 |

DIAGNOSIS

1. **History of exposure** from family members or friends
2. **Empty container** can be good source of information for diagnosis if available at site of accident.
3. Estimation of **plasma or RBC cholinesterase** level(RBC cholinesterase level is less than 50% of normal.)
4. **P-Nitrophenol** is a **metabolite of many OP's which is excreted in urine** and can be used as a qualitative test.

1. Ancillary investigation include:-

- a. Leukocytosis
- b. High Hematocrit
- c. Anion gap acidosis
- d. hyperglycemia
- **Chest radiograph** may reveal **pulmonary edema** but typically adds little to the clinical management of a poisoned patient.
- CT-scan
- Thin Layer Chromatography (TLC)
- High performance thin layer chromatography (HPLC)

OTHER TEST

- **ECG findings** include prolonged QTc interval, elevated ST segments, and inverted T waves. Although **sinus tachycardia** is the most common finding in the poisoned patient, **sinus bradycardia with PR prolongation** can develop with **increasing toxicity** due to excessive parasympathetic activation.

MANAGEMENT

MANAGEMENT

- **Emergency and supportive care :**
- **Endotracheal intubation and mechanical ventilation** may be necessary in patients with organophosphate poisoning for airway protection and management of bronchorrhea and seizures.
- **Central venous access and arterial lines** may be needed to treat the patient with organophosphate toxicity who requires multiple medications and blood-gas measurements.

DECONTAMINATION

- Patient washed thoroughly with soap and water if skin spillage
- Wash with **cold water for 5 minutes and then with hot** water from head to toe using non-germicidal soap
- **Ocular exposure-irrigation** with normal saline or Ringer's solution.

- **Gastric lavage** is the most common form of decontamination for OP poisoning despite the **absence of randomized controlled trials to confirm benefit.**
- Lavage should be considered only if the patient arrives within **1 hour** of ingesting poison
- **Ipecacuanha-induced emesis should not** be used in OP poisoning.
- Patients poisoned with OP can rapidly become unconscious, risking **aspiration** if ipecacuanha has been given.

SUPPORTIVE MEASURES

- Maintain **airway patency**
- Control of **blood glucose**
- **Endotracheal intubation and mechanical ventilation** may be necessary
- Monitor pulse oximetry or arterial blood gases to determine need for **supplemental oxygen**.
- Oxygenation
- Administer **IV fluids** to replace losses
- Patient should be placed in the **left lateral position**, with the **neck extended**.
- This position reduces risk of aspiration; helps keep the airway patent, and could decrease pyloric emptying and absorption of poison

ANTIDOTE

The mainstays of medical therapy in organophosphate (OP) poisoning include :

1. Atropine,
2. Pralidoxime (2-PAM), and
3. Benzodiazepines (eg, diazepam)

Intravenous **Glycopyrrolate** or **Diphenhydramine** may provide an alternative **centrally acting anticholinergic agent** used to treat muscarinic toxicity if atropine is unavailable or in limited supply.

Atropine



Muscarinic Effects

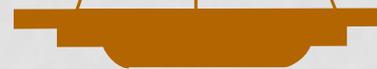
**Heart rate
Sweating
Secretion
Pupils**



2 PAM



AChE Inhibitions



*Nicotinic
Muscarinic*



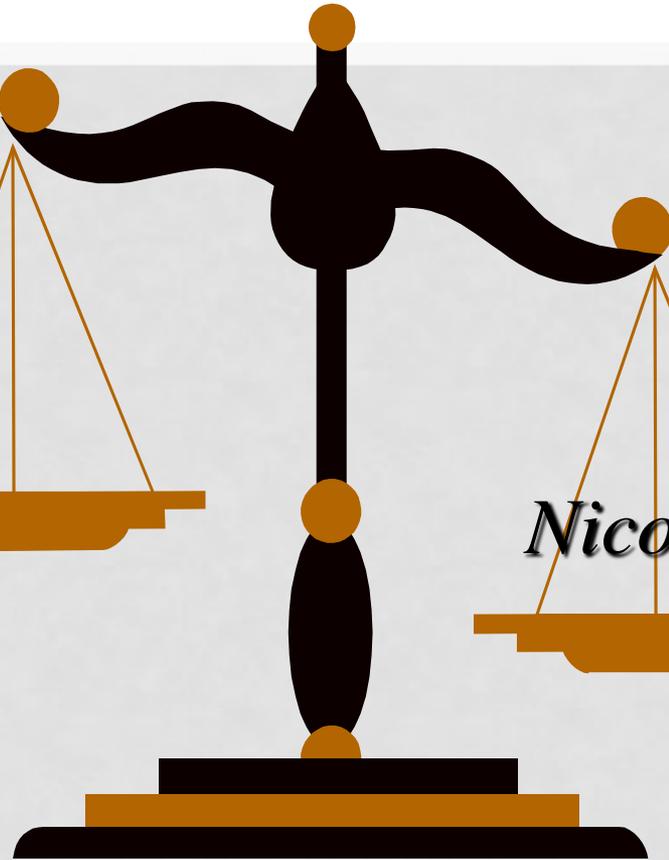
2 PAM



Nicotinic Effects



Motor Power
+ *(Muscarinic Effects)*



ATROPINE

- **Atropine** : Atropine—It is a **competitive antagonist of acetylcholine** at the muscarinic postsynaptic membrane and in the CNS.
- It has **no effect on muscle weakness or paralysis**

DOSE

Diagnostic dose:

- Adult: 1 mg IV or IM;
- Child—0.25 mg (about 0.01 mg/kg IV or IM

Therapeutic dose:

- Adult :1 to 2 mg IV or IM
- Child: 0.05 mg/kg IV (child);

Every 15 minutes until the endpoint is reached

- Endpoint: Drying up of tracheobronchial secretions

- Atropine can also be administered as an **IV infusion** after the initial bolus dose, at a rate of **0.02 to 0.08 mg/kg/hr**.
- Once the **endpoint has been reached**, the **dose should be adjusted** to maintain the effect for at least 24 hours
- **Atropinisation** must be maintained until all of the absorbed **organophosphate has been metabolised**.
- This may require administration of 2 to 2,000 milligrams of atropine over several hours to weeks

- Atropine therapy must be **withdrawn slowly** to prevent **recurrence or rebounding of symptoms**, often in the form of pulmonary edema
- Effects of **atropine overdosing**-fever, warm dry skin, inspiratory stridor, irritability, and dilated and unresponsive pupils
- **Adverse effects** : Atrial arrhythmias, AV dissociation, multiple ventricular ectopics, photophobia, raised intraocular pressure, hyperpyrexia, hallucinations, and delirium

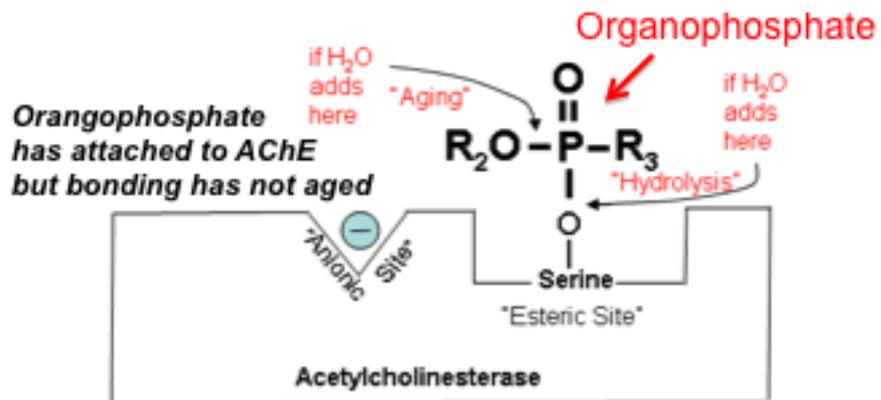
PRALIDOXIME (PYRIDINE-2-ALDOXIME METHIODIDE; 2-PAM)

- Pralidoxime **competes for the phosphate moiety of the organophosphorus compound** and releases it from the acetylcholinesterase enzyme, thereby liberating the latter and reactivating it
- This reactivation is clinically **most apparent at skeletal neuromuscular junctions**, with **less activity at muscarinic sites**.
- Current recommendation is **administration within 48 h of OP poisoning**.

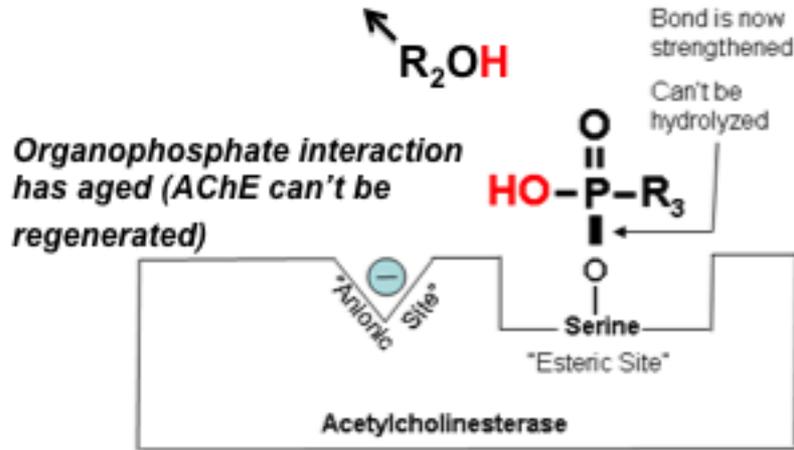
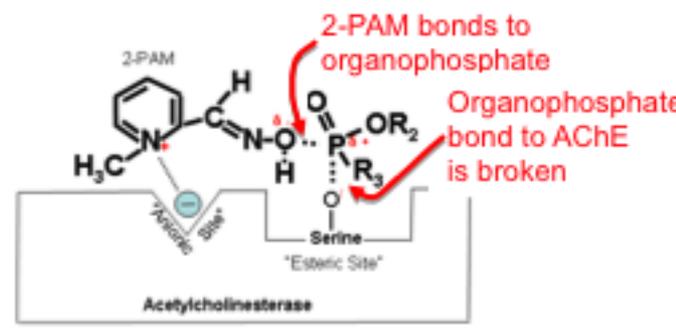
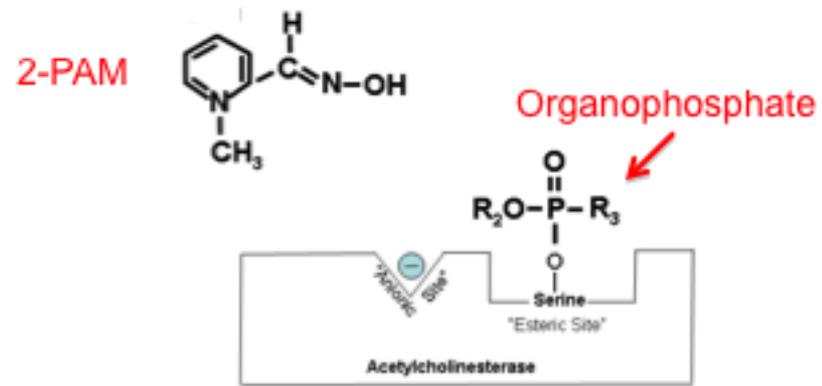
- Because it **does not significantly relieve depression of respiratory center or decrease muscarinic effects of AChE poisoning,**
- Need to **administer atropine concomitantly** to block these effects of OP poisoning.

Organophosphate Aging – chemical stabilization of phosphate bond to AChE occurs over time

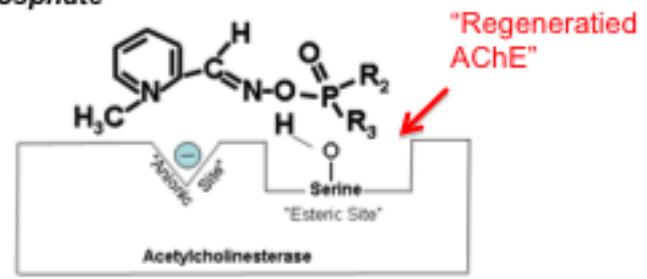
Pralidoxime (2-PAM) prevents aging & regenerates AChE



The rate of aging is unique for each organophosphate compound, and can occur over minutes to days depending on the agent



The departure of the R₂ alkyl group (aging) results in increased electron sharing between the phosphate group of the organophosphate & the serine on AChE. This bond can't be broken by 2-PAM.



DOSE

- For adults—1 to 2 gm in 100 to 150 ml of 0.9% sodium chloride, given IV over 30 minutes
- This can be repeated after 1 hour, and subsequently every 6 to 12 hours, for 24 to 48 hours
- Alternatively, a 2.5% concentration of pralidoxime can be given as a **loading dose** followed by a maintenance dose

- **Serious intoxication** may require continuous infusion of **500 mg/hr** in adults.
- **Maximum dose** should not exceed 12 gm in a 24 hour period.
- **Infusion over a period of several days** may be necessary and is generally well tolerated
- The **WHO currently recommends** an initial bolus of at least 30 mg/kg, followed by an infusion of more than 8 mg/kg /hr

- It is estimated that a **plasma concentration** of at least 4 mg/L may be necessary for pralidoxime to be effective
- **For children**—20 to 40 mg/kg to a maximum of 1 gm/dose given IV, and repeated every 6 to 12 hours for 24 to 48 hours

- **Adverse effects:** Rapid administration can cause tachycardia, laryngospasm, and even cardiac or respiratory arrest
- **Other adverse effects** include drowsiness, vertigo, headache, and muscle weakness

- Oximes may not be useful, particularly for **late presentations of dimethyl OP** and those with a **large excess of OP** that simply reinhibits reactivated enzymes.

DIAZEPAM

- Diazepam prevents **convulsions and cardiac damage**
- **Addition of diazepam** to atropine and 2-PAM **improves survival**
- it **prevent the late effects** caused by seizure-induced brain damage

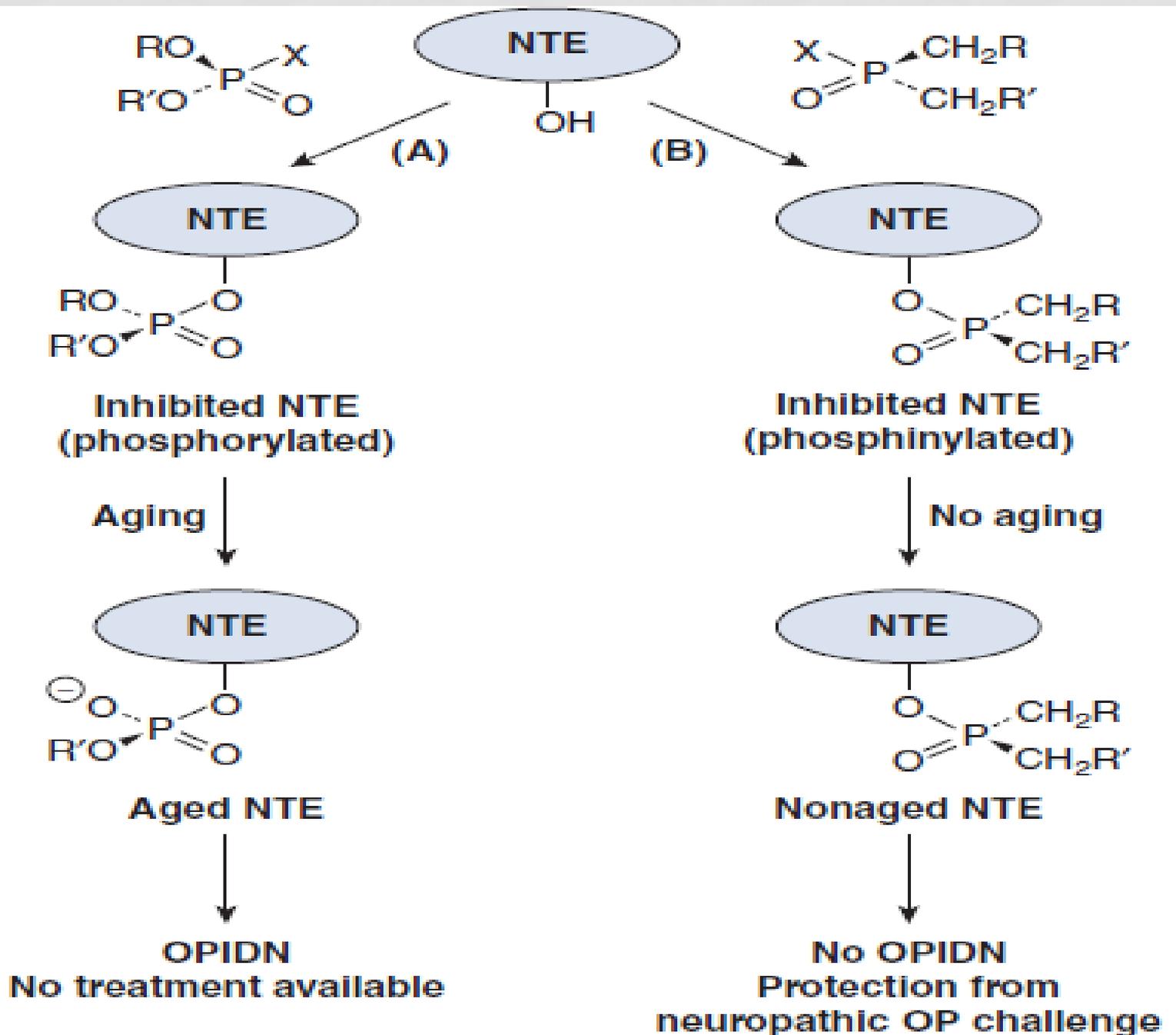
- Dose: For adults—5 to 10 mg IV slowly, every 15 minutes, upto a maximum of 30 mg
- For children—0.25 to 0.4 mg/kg IV slowly, every 5 to 10 minutes, upto a maximum of 10 mg
- If diazepam is ineffective, phenytoin or phenobarbitone can be used instead

FOR INTERMEDIATE SYNDROME

- Managed by supportive measures, since it does not respond to oximes or atropine.
- Consideration of artificial respiration are recommended.

FOR OPHOSPHATE-INDUCED DELAYED NEUROPATHY

- This syndrome also **does not respond** to either **oximes or atropine**
- There is **no known treatment for OPIDN**
- Standard therapy should be accompanied with neuroprotective drugs like corticosteroids for prevention
- **Protease inhibitors** have been useful in **protecting the neuropathy target esterase** and preventing the establishment of delayed neuropathy



OTHER THERAPIES

Magnesium Sulfate

- **Blocks calcium channels** and thus reduces acetylcholine release
- **Reduces CNS overstimulation** resulting from N-methyl D-aspartate receptor (NMDAR)
- Intravenous MgSO₄ (4 g) given in the first day after admission have been shown to **decrease hospitalization period and improve outcomes**

Advanced Neuroprotective Drugs

- **Ketamine**, a noncompetitive **NMDAR antagonist**, can be used until 1 hour following nerve agent-induced seizures
- **Tezampanel**, another **glutamate receptor antagonist** useful against soman-induced seizures and neuropathy

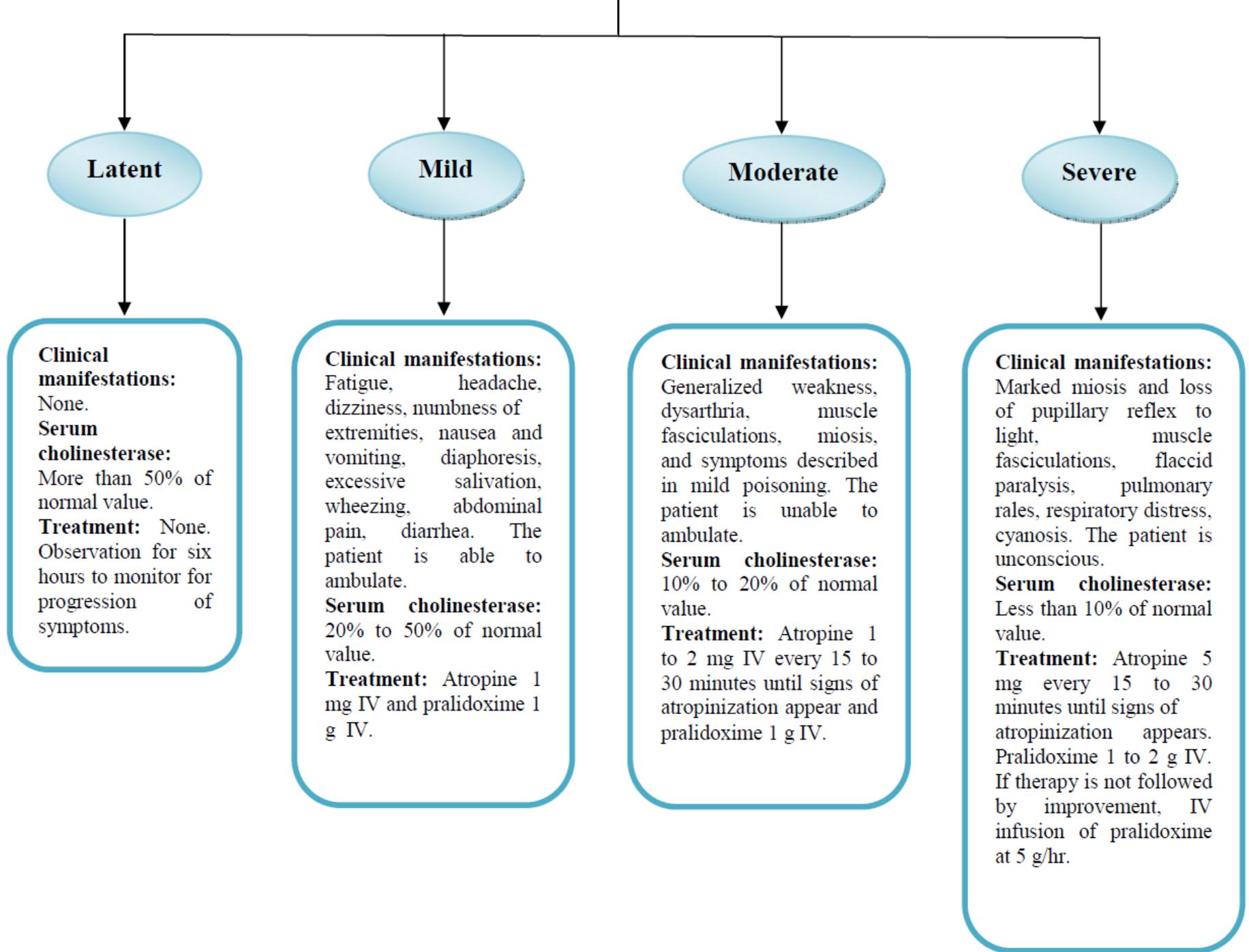
Gacyclidine

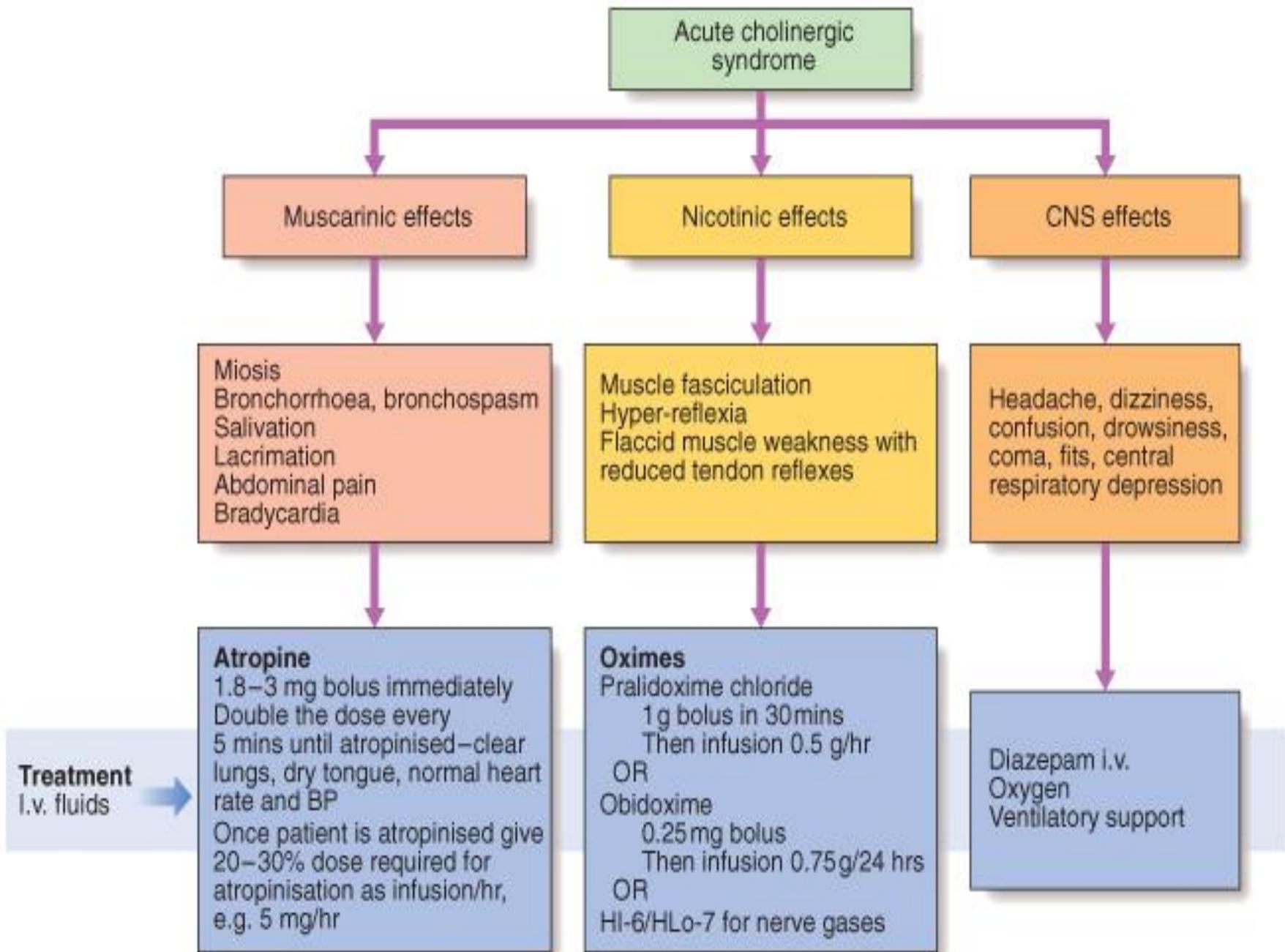
- **Antiglutamatergic** compound that was proved to be beneficial in conjunction with atropine, pralidoxime, and diazepam in nerve agents poisoning
- **Gacyclidine inhibited the neuropathology** that occurred 3 weeks following exposure in animals
- In **severe nerve agent poisoning**, gacyclidine can be a useful adjuvant therapy along with standard therapy.

- Using hemodialysis, **hemoperfusion or hemofiltration is not clear.**
- In a **recent report**, it was claimed that hemofiltration after dichlorvos poisoning had revealed beneficial **therapeutic effects.**

FUTURE DRUGS

- **Huperzine A and ZT-1 :**
- HupA has been proven to be a powerful, highly specific, and reversible inhibitor of acetylcholinesterase
- **ZT-1** has similar properties to HupA regarding the ability to cross the blood–brain barrier, its oral bioavailability, and its longevity of action.
- **Phosphotriesterases (PTEs):** detoxification of OPs





SUMMARY AND COMMENT | EMERGENCY MEDICINE

March 7, 2008

Activated Charcoal Has No Benefit in Organophosphate Overdose

Kristi L. Koenig, MD, FACEP, FIFEM reviewing Eddleston M et al. Lancet 2008 Feb 16. Eyer P and Eyer F. Lancet 2008 Feb 16.

As with other types of overdose, activated charcoal fails to make a difference.

Early activated charcoal administration was once considered a mainstay of treatment for patients with acute overdose, based on the belief that it adsorbs toxins in the stomach and therefore reduces absorption and systemic toxicity. However, studies have failed to show any benefit from activated charcoal, even from acute or delayed administration for poisons with enterohepatic circulation, and aspiration of charcoal carries serious consequences.

In a prospective, randomized, controlled trial, 4632 patients aged 14 years or older who presented to three hospitals in Sri Lanka after intentional overdoses received no charcoal, a single dose of charcoal (50 g), or multiple doses of charcoal (50 g every 4 hours for 6 doses). Most patients had ingested pesticides (51%) or yellow oleander seeds (36%). Median time between ingestion and admission was 4.2 hours. The mortality rate was 6.7% overall and did not differ among treatment groups. In addition, the proportion of patients who needed assisted ventilation, the median duration of ventilation, and the proportion of patients who developed seizures or dysrhythmias were similar among groups.

Kristi L. Koenig, MD, FACEP, FIFEM

Associate Editor
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