INSECTICIDES

BY DR. SWATHI SWAROOPA. B

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

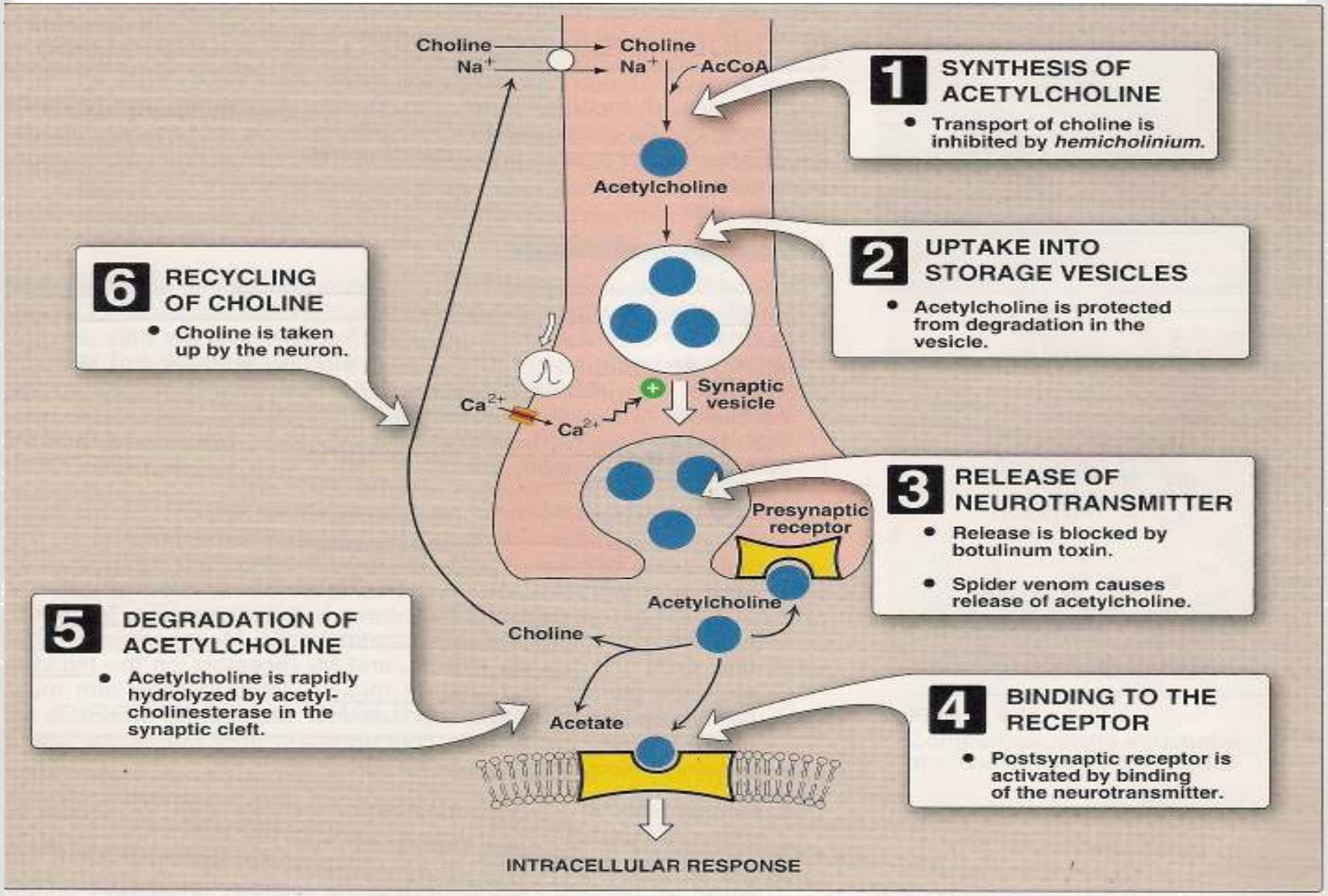
- Organophosphorus compounds also known as cholinesterase inhibitors, and are widely used pesticides that may cause poisonings after accidental or suicidal exposure.

- 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



MECHANISM OF ACTION OF ORGANOPHOSPATE 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

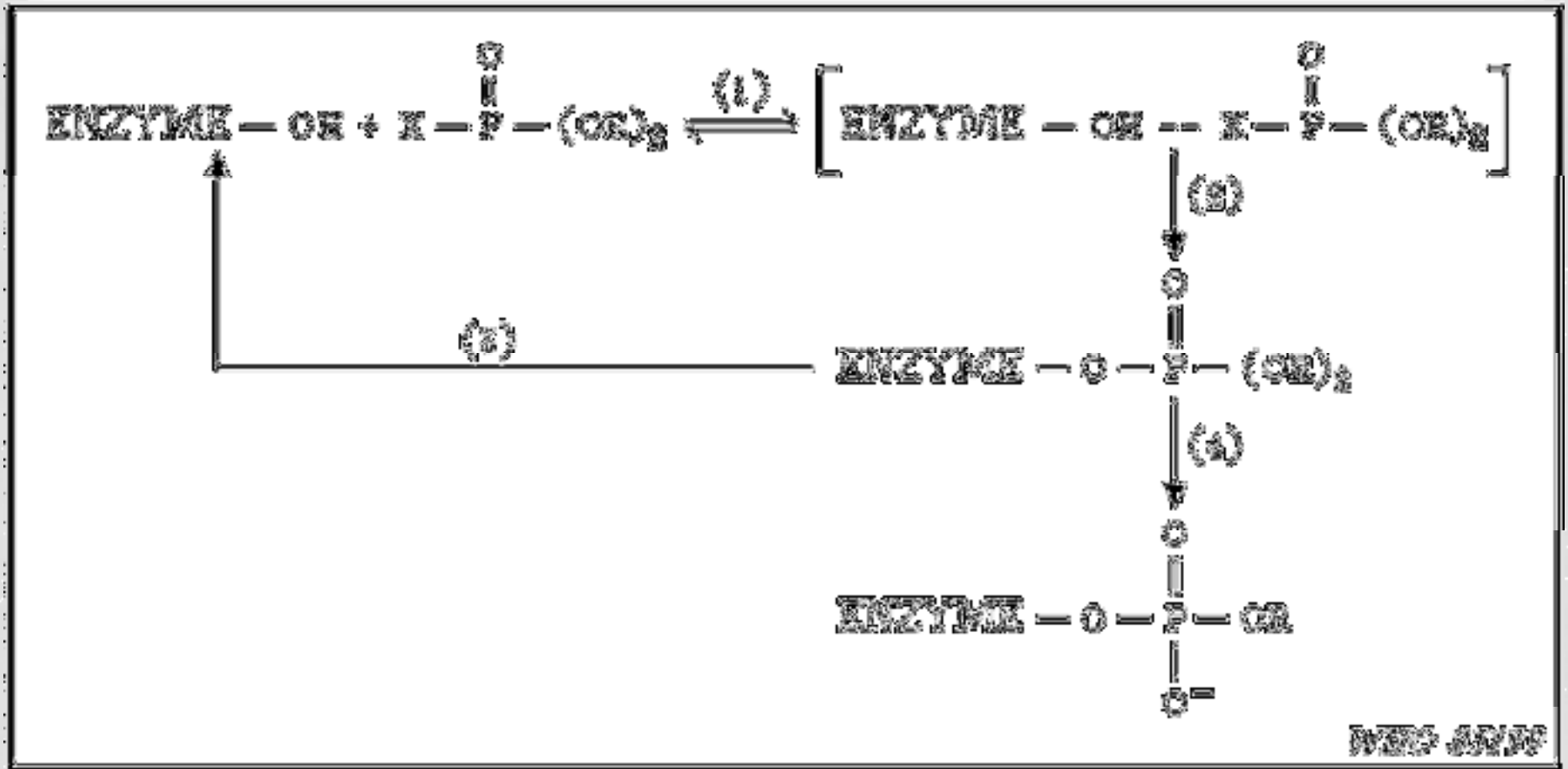
↓

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

↓

Overstimulation of cholinergic receptors

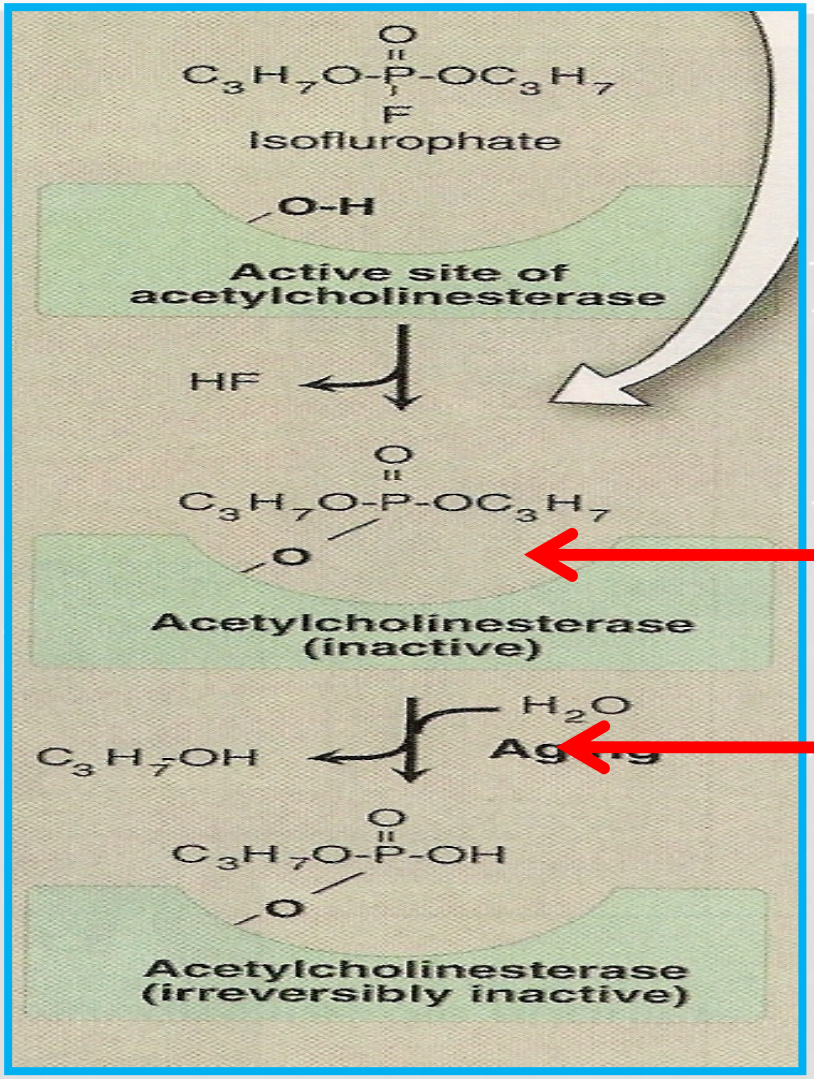
MECHANISM OF ACTION OF ORGANOPHOSPHORUS POISONING



Inhibition of an esteratic 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

- 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, Chlorpyriphos, 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

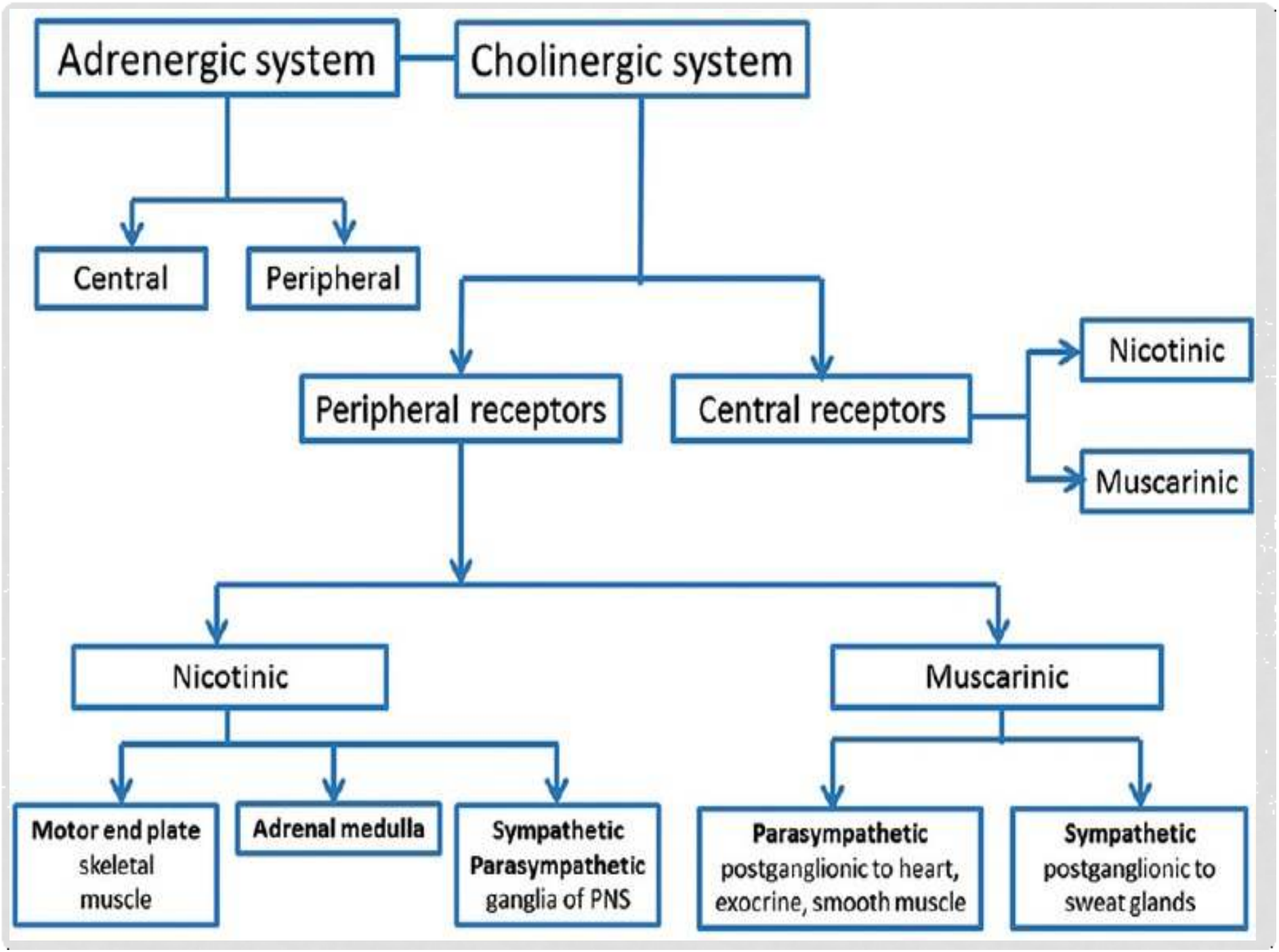
- OPs, after entering an organism, are metabolised with phase I and II enzymes
- Phase I of OP metabolism involves oxidation and hydrolysis:
- Oxidation is the most important reaction in the activation of the OP thiono form to form active inhibitors of AcHE
- Hydrolysis of OPs takes place after oxidation, 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 detoxificating 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
    - Muscarnic, 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	Tachycardia, hypertension
		Adrenal medulla	
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

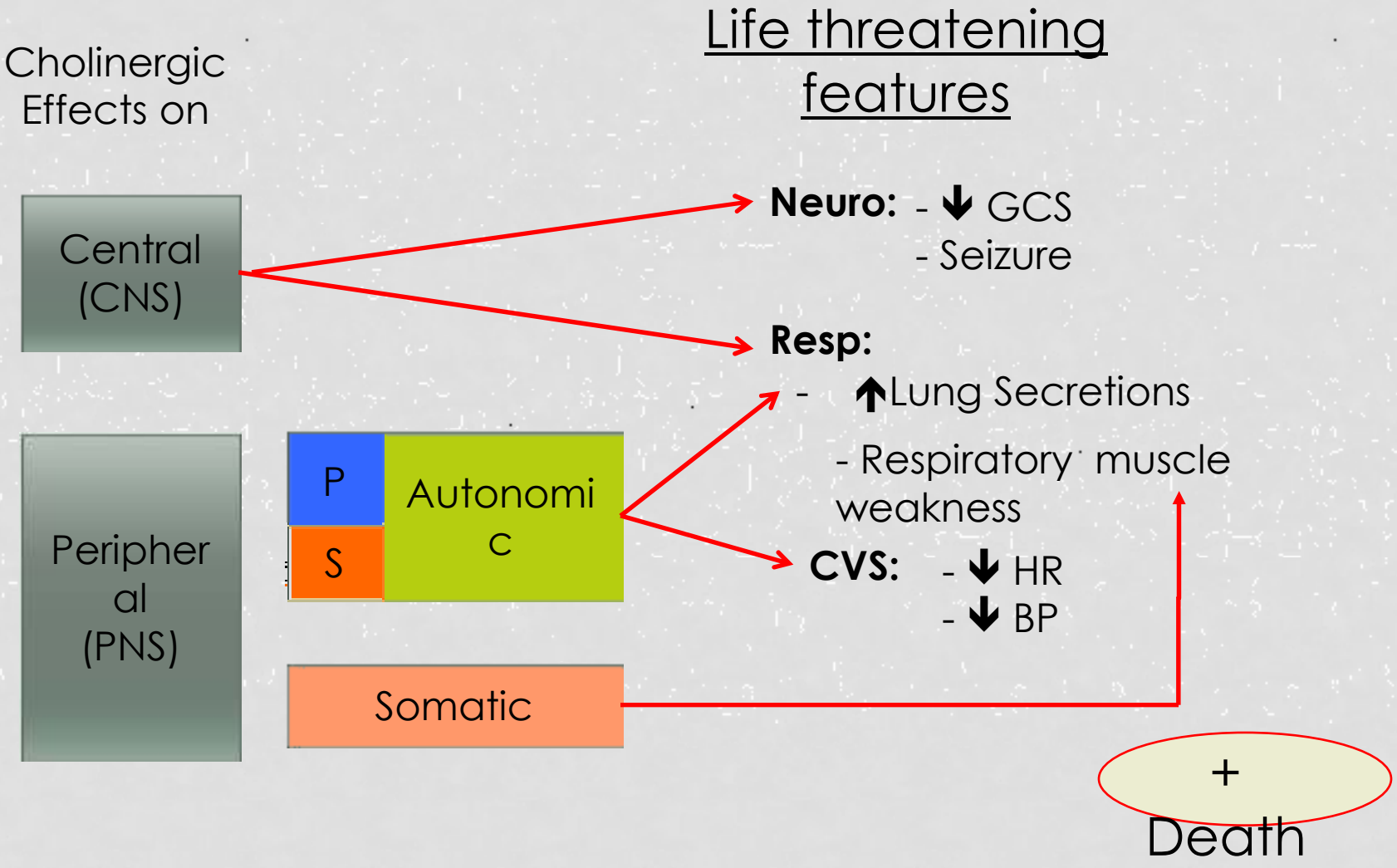
*M1 receptors play a critical role in cognitive function; M3 receptor effect predominates in the pupils, airway smooth muscles and mucus glands. Nicotinic receptors are sub-typed as N1 or Nm receptors and N2 or Nn receptors. Muscarinic receptors are sub-typed from M1 to M5

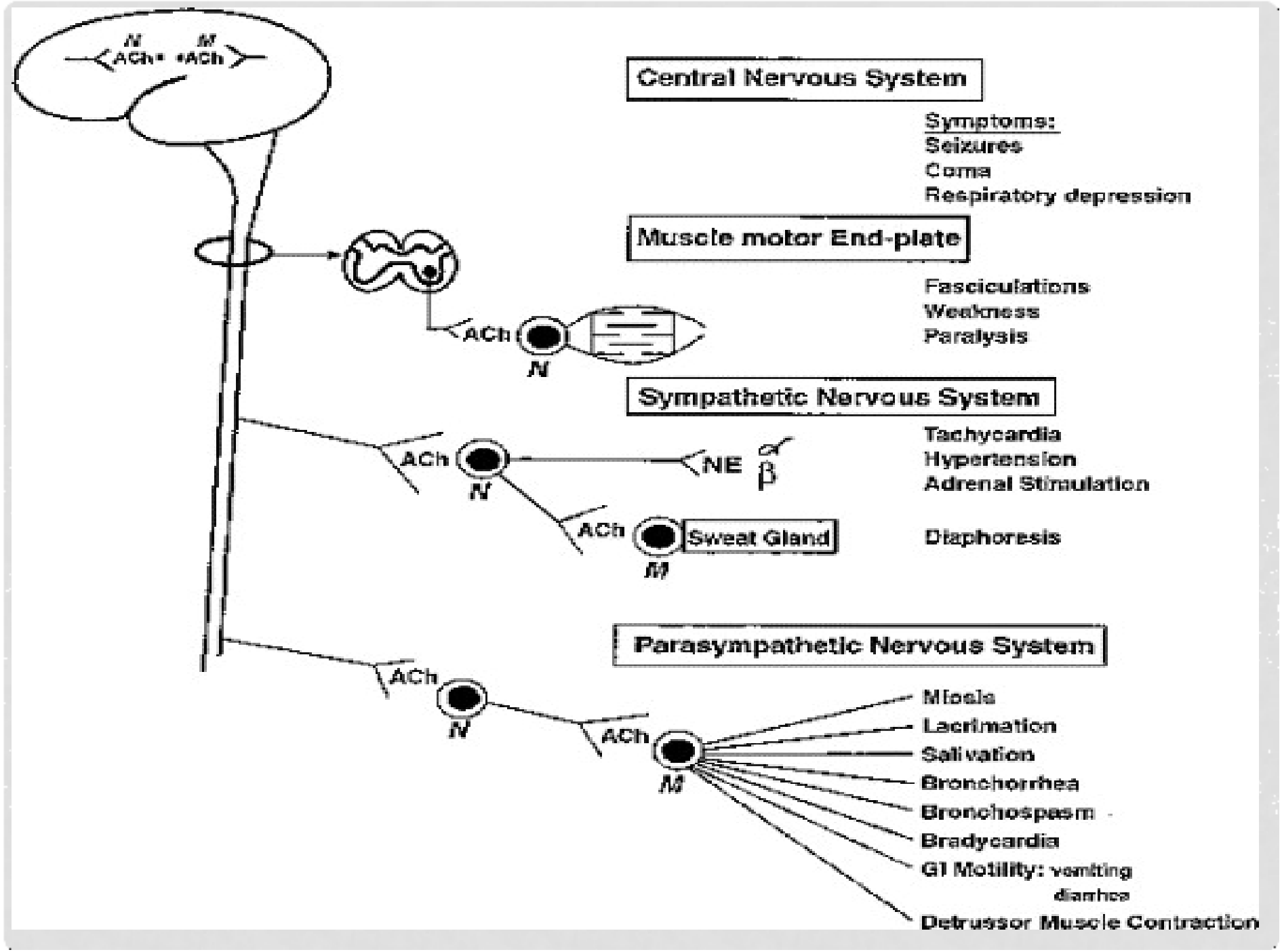
Time of manifestation	Mechanism	Manifestation
Acute (minutes to 24-h)	Nicotinic receptor action	Weakness, fasciculations, cramps, paralysis
	Muscarinic receptor action	Salivation, lacrimation, urination, defecation, gastric cramps, emesis, bradycardia, hypotension, miosis, bronchospasm
	Central receptors	Anxiety, restlessness, convulsions, respiratory depression
Delayed (24-h to 2-week)	Nicotinic receptor action	Intermediate syndrome
	Muscarinic receptor action	Cholinergic symptoms-bradycardia, miosis, salivation
	Central receptors	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




N
ACh
M
ACh
Central Nervous System
Symptoms:
Seizures
Coma
Respiratory depression
Muscle motor End-plate
Fasciculations
Weakness
Paralysis
ACh
N
Sympathetic Nervous System
Tachycardia
Hypertension
Adrenal Stimulation
ACh
N
NE
α
β
ACh
Sweat Gland
M
Diaphoresis
Parasympathetic Nervous System
ACh
N
ACh
M
Miosis
Lacrimation
Salivation
Bronchorrhea
Bronchospasm
Bradycardia
GI Motility: vomiting
diarrhea
Detrussor Muscle Contraction

CLINICAL MANIFESTATIONS OF OP POISONING

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

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,Bronchorrhea
- 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

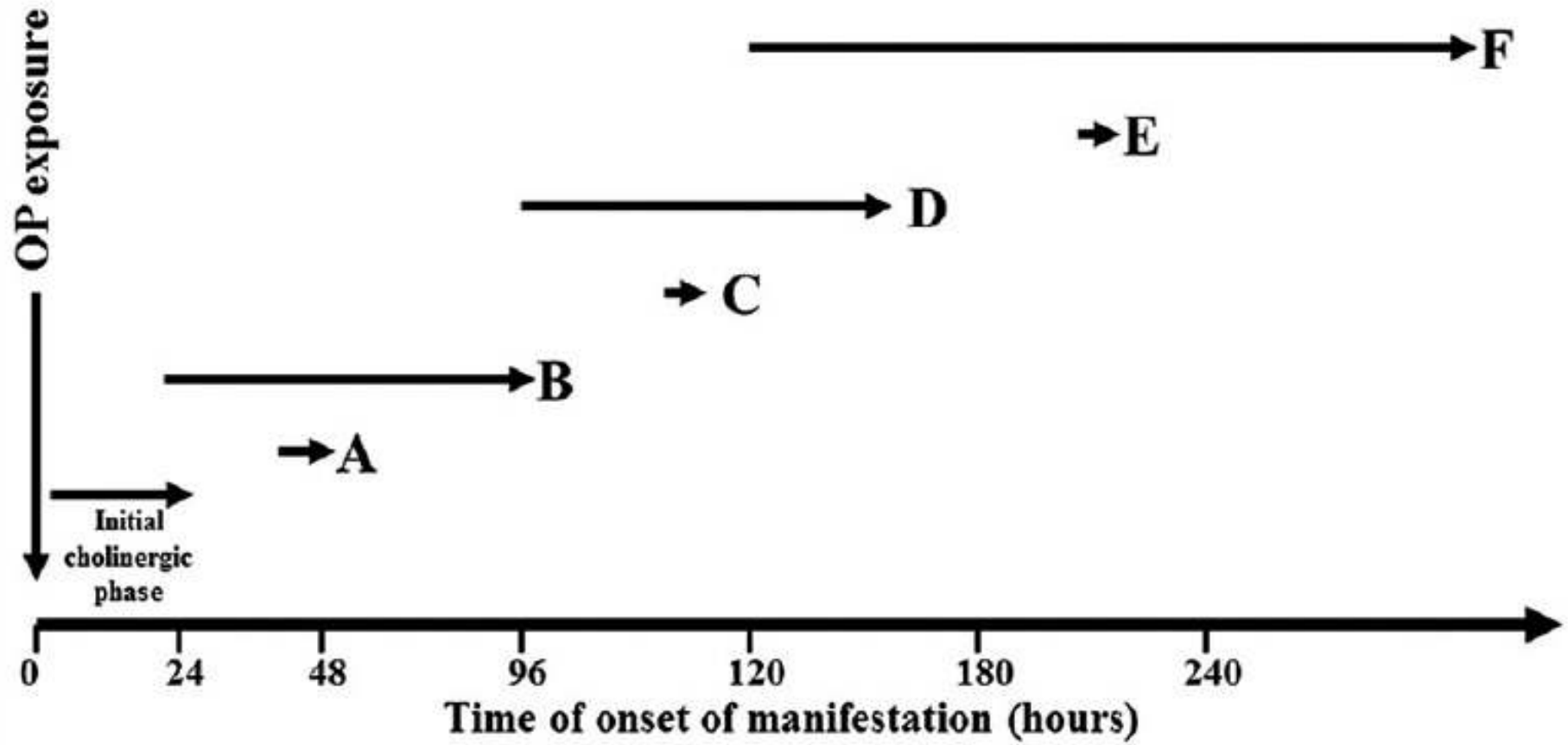
MUSCARINIC EFFECTS BY ORGAN SYSTEMS

- **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 **1to 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.

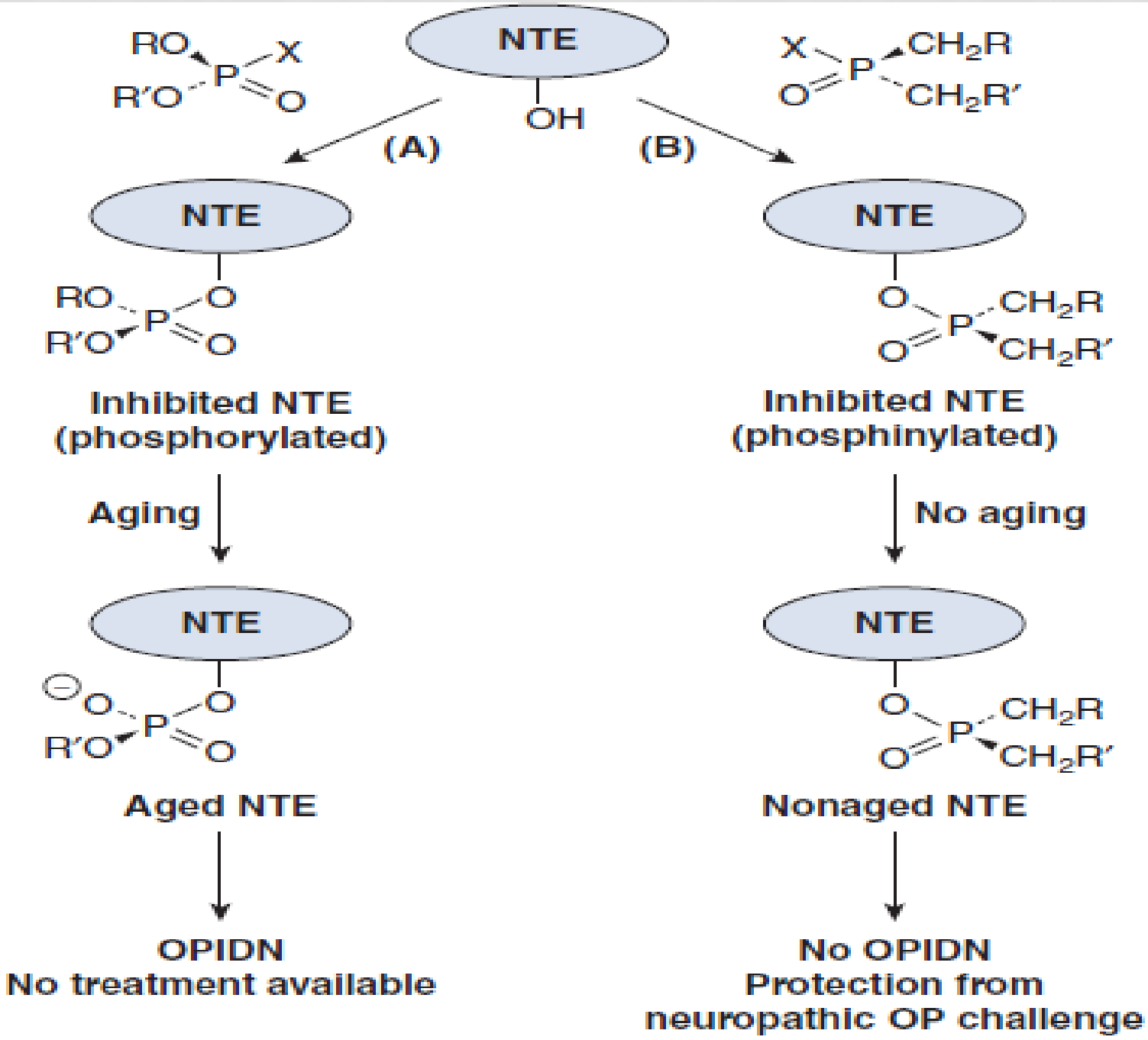
DELAYED SYNDROME

- 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 (chloropyriphos)
- A distinct acute or intermediate phase may not always precede its development


NTE
OH
(A)
(B)
Inhibited NTE
(phosphorylated)
Aging
Aged NTE
OPIDN
No treatment available
Inhibited NTE
(phosphinylated)
No aging
Nonaged NTE
No OPIDN
Protection from
neuropathic OP challenge

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

Paralysis :

- Type I: This condition is described as acute paralysis secondary to continued depolarization at the neuromuscular junction.

- Type II: (intermediate syndrome):develop 24-96 hours after resolution of acute organophosphate poisoning symptoms and manifests commonly as paralysis and respiratory distress.

- Involves weakness of proximal muscle groups, neck, and trunk, with relative sparing of distal muscle groups.
- Type III: Organophosphate-induced delayed polyneuropathy (OPIDP) occurs 2-3 weeks after exposure to large doses of certain organophosphates (OPs) and is due to inhibition of neuropathy target esterase. Distal muscle weakness with relative sparing of the neck muscles, cranial nerves, and proximal muscle groups characterizes OPIDP. Recovery can take up to 12 months

- **Case of Chronic poisoning:-**It usually occurs as an occupational hazard in farmers, especially those who engaged in pesticide spraying of crops. Route of exposure is usually inhalation or contamination of skin. The following are the main features:

➢ **Polyneuropathy:-**paresthesias(Abnormal skin sensations), muscle cramps, weakness.

➢ **CNS effects:-**drowsiness, confusion**,** irritability, anxiety, etc.

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 should be 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.

- **Health care providers** must avoid contaminating themselves while handling patients. Need to use personal protective equipment, such as neoprene gloves and gowns, when decontaminating patients because hydrocarbons can penetrate nonpolar substances such as latex and vinyl. Use charcoal cartridge masks for respiratory protection when decontaminating patients who are significantly contaminated.
- Irrigate the eyes of patients who have had ocular exposure using isotonic sodium chloride solution or lactated Ringer's solution. Morgan lenses can be used for eye irrigation.

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

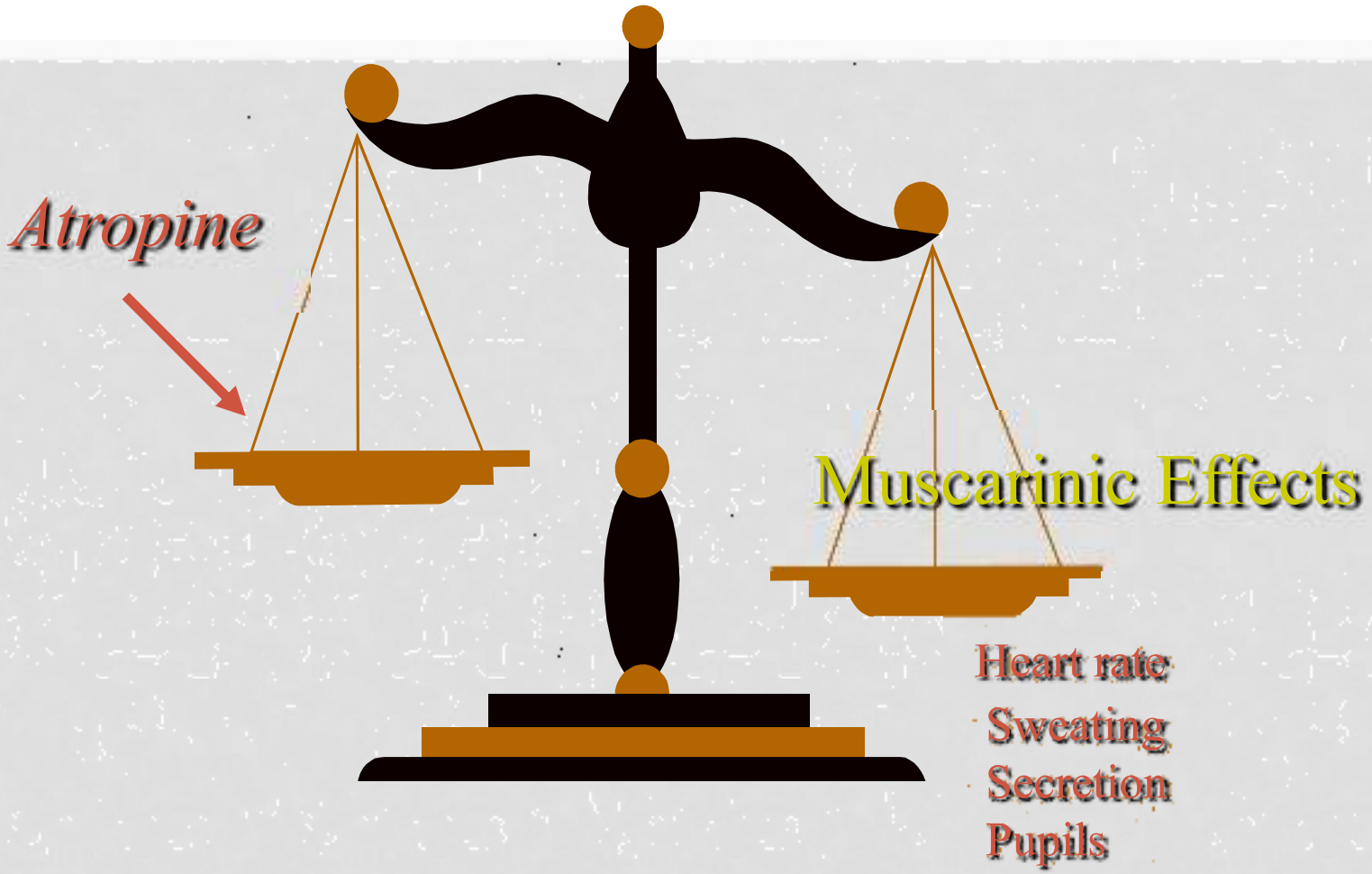
The mainstays of medical therapy in organophosphate (OP) poisoning include :

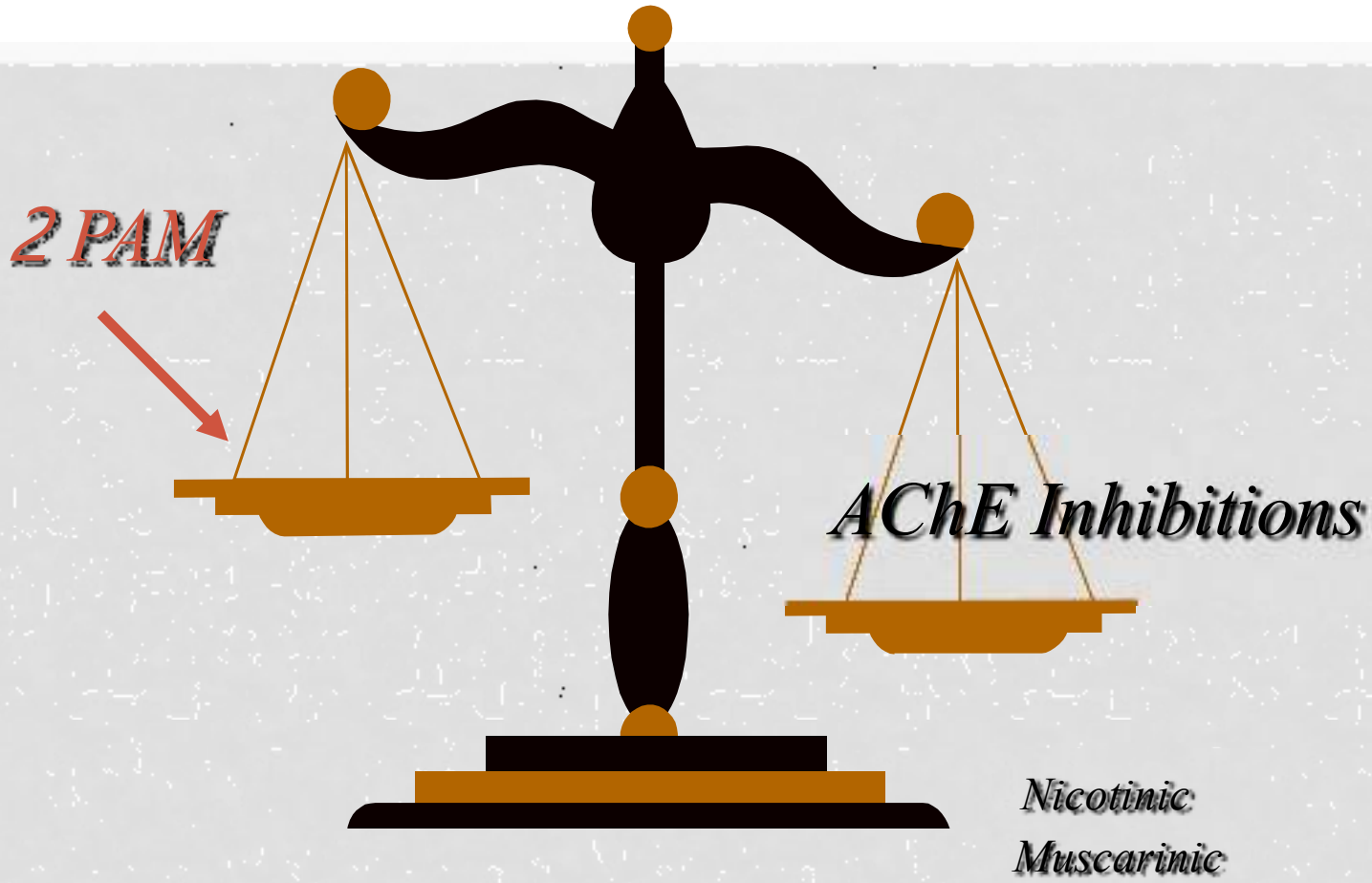
1. **Atropine,**
2. **Pralidoxime (2-PAM), and**
3. **Benzodiazepines (eg, diazepam)**

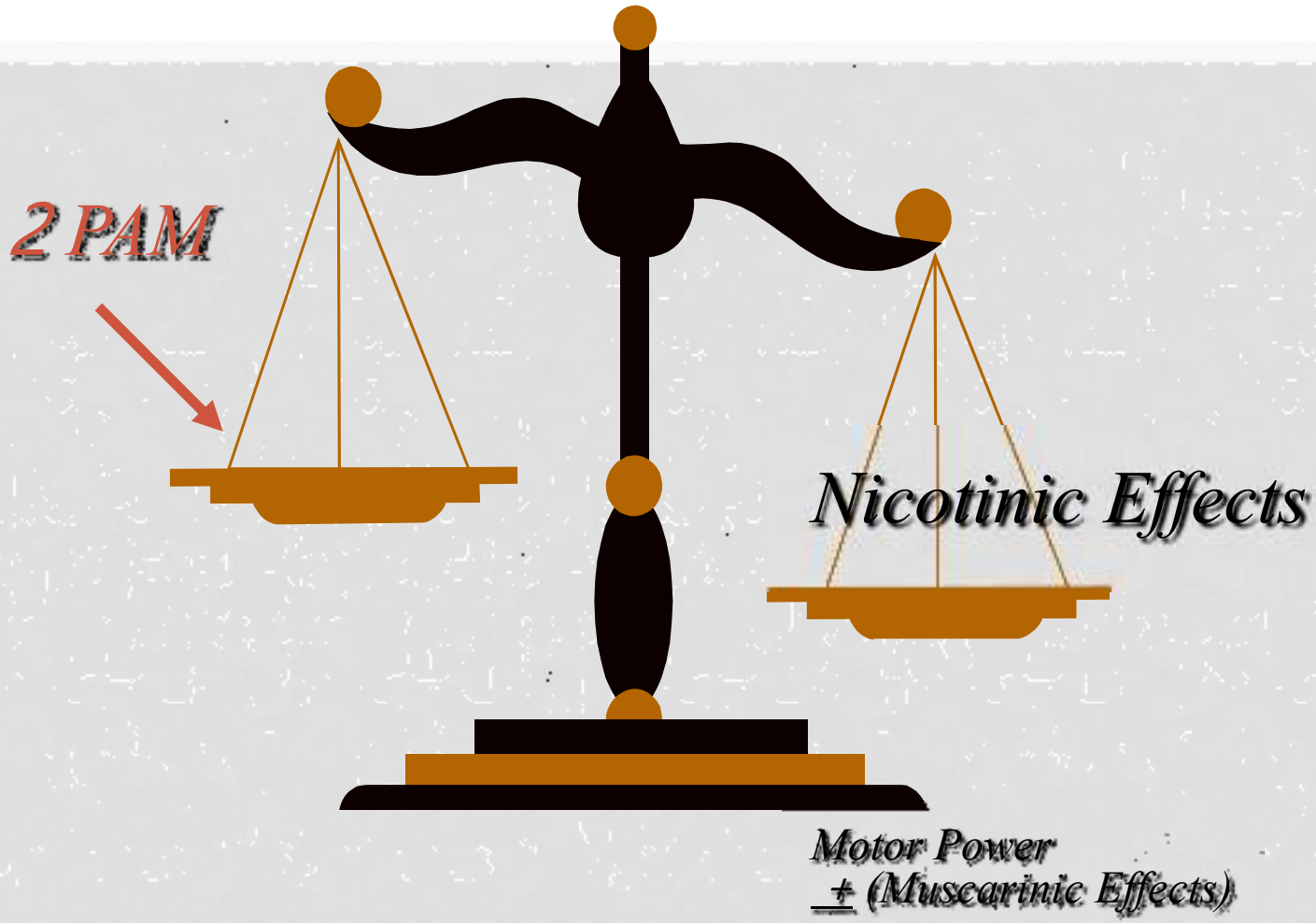
If atropine is unavailable or in limited supply, intravenous glycopyrrolate or diphenhydramine may provide an alternative anticholinergic agent for treating muscarinic toxicity; however, glycopyrrolate does not cross the blood-brain barrier and cannot treat central effects of OP poisoning

- A single-center, randomized, single-blind study by Pajoumand et al found a benefit to magnesium therapy in addition to standard oxime and atropine therapy in reducing hospitalization days and mortality rate in patients with OP poisoning

- The mechanisms appear to be inhibition of acetylcholine (ACh) and OP antagonism


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**

- **Optimizing oxygenation prior to the use of atropine is recommended to minimize the potential for dysrhythmias.**

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

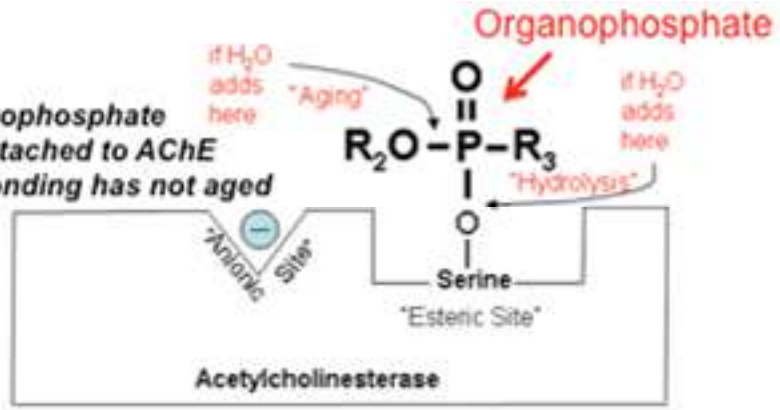
- This reactivation is clinically **most apparent** at **skeletal neuromuscular junctions,** with **less activity at muscarinic sites**.

- Current recommendation is **administration within 48 h of OP** poisoning.

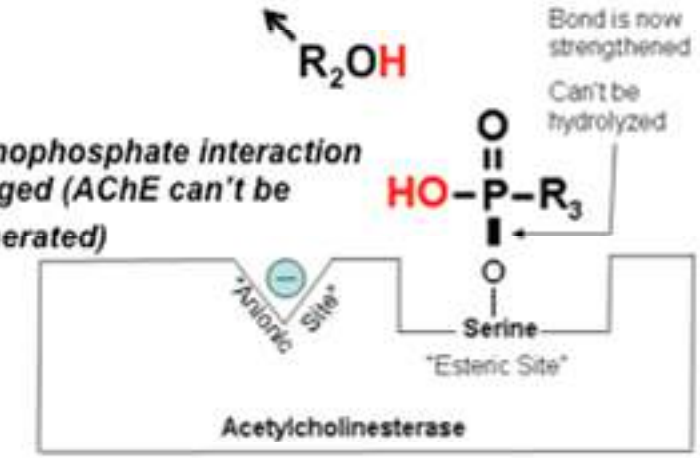
- Because it **does not significantly relieve depression of respiratory center or decrease muscarinic effects of AChE** poisoning,

- Need to **administer atropine concomitantly** to block these effects of OP poisoning.

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

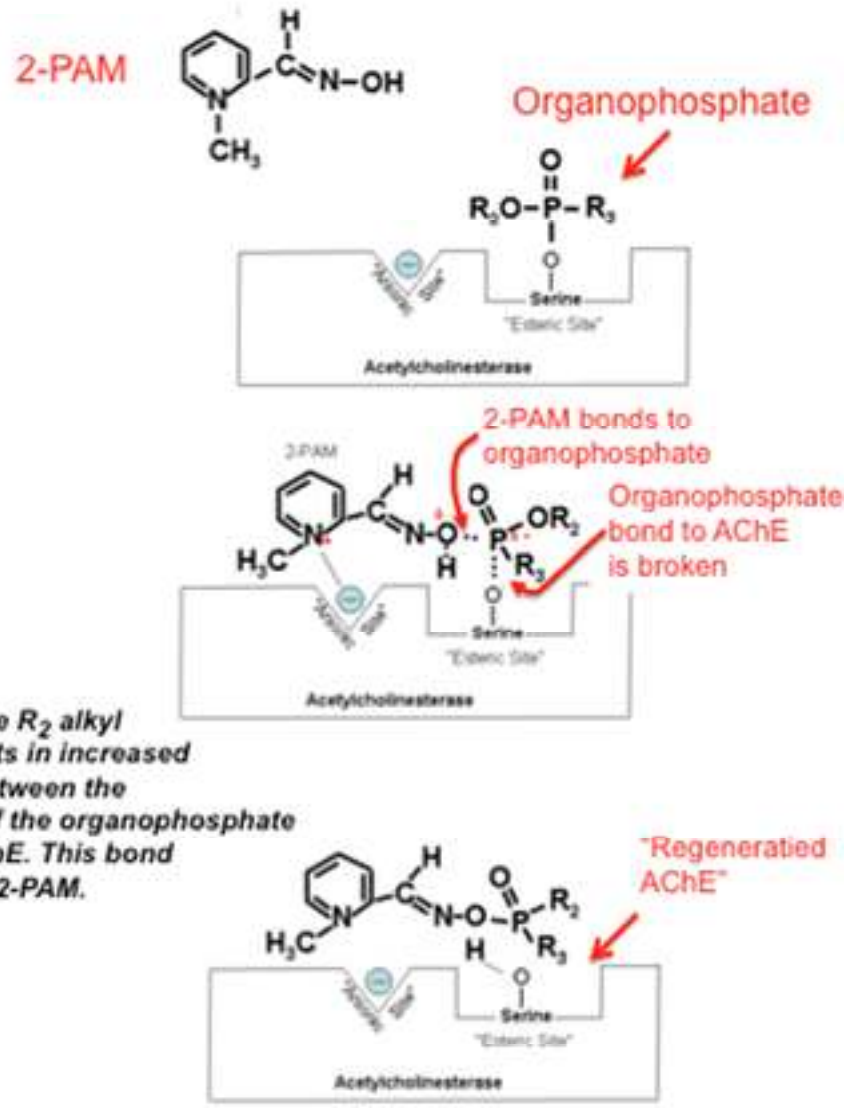


The rate of aging is unique for each organophosphate compound, and can occur over minutes to days depending on the agent



The departure of the R_2 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.

Pralidoxime (2-PAM) prevents aging & regenerates AChE



Modifed from: CDC Case Studies in Environmental Medicine
http://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=23

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

- **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

- The controversy continued when other authors observed more respiratory complications and higher mortality rates with use of high-dose 2-PAM. Low-dose (1-2 g slow IV) 2-PAM is the current recommendation.

- **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.

- Glycopyrrolate : antimuscarinic agent to reduce salivary, tracheobronchial, and pharyngeal secretions.
- Does not cross the BBB. Can be considered in patients at risk for recurrent symptoms (after initial atropinization) but who are developing central anticholinergic delirium or agitation.

DIAZEPAM

- Diazepam prevents **convulsions**
- **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

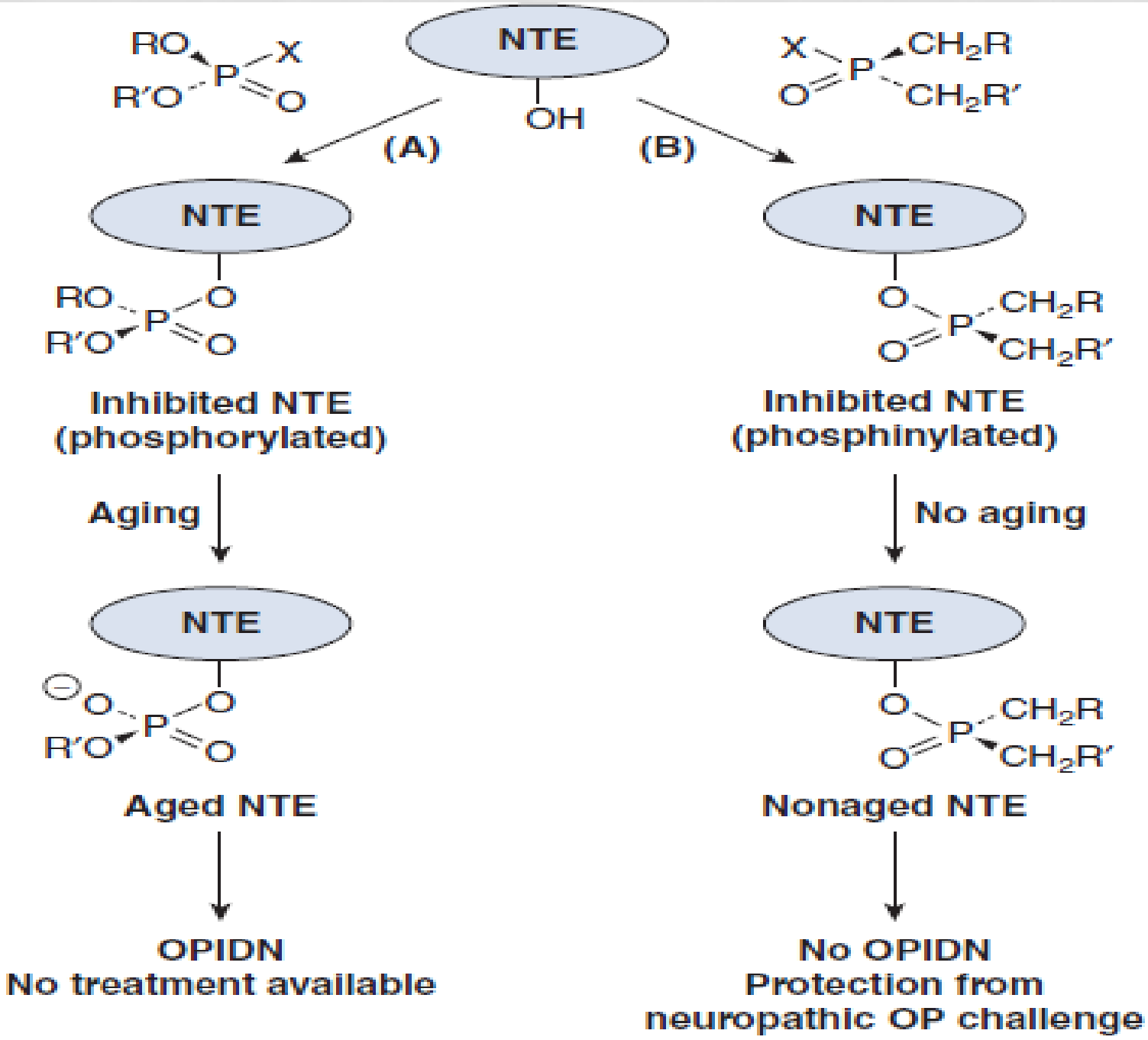
FOR INTERMEDIATE SYNDROME

- 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


NTE
OH
(A)
(B)
Inhibited NTE
(phosphorylated)
Aging
Aged NTE
OPIDN
No treatment available
Inhibited NTE
(phosphinylated)
No aging
Nonaged NTE
No OPIDN
Protection from
neuropathic OP challenge

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

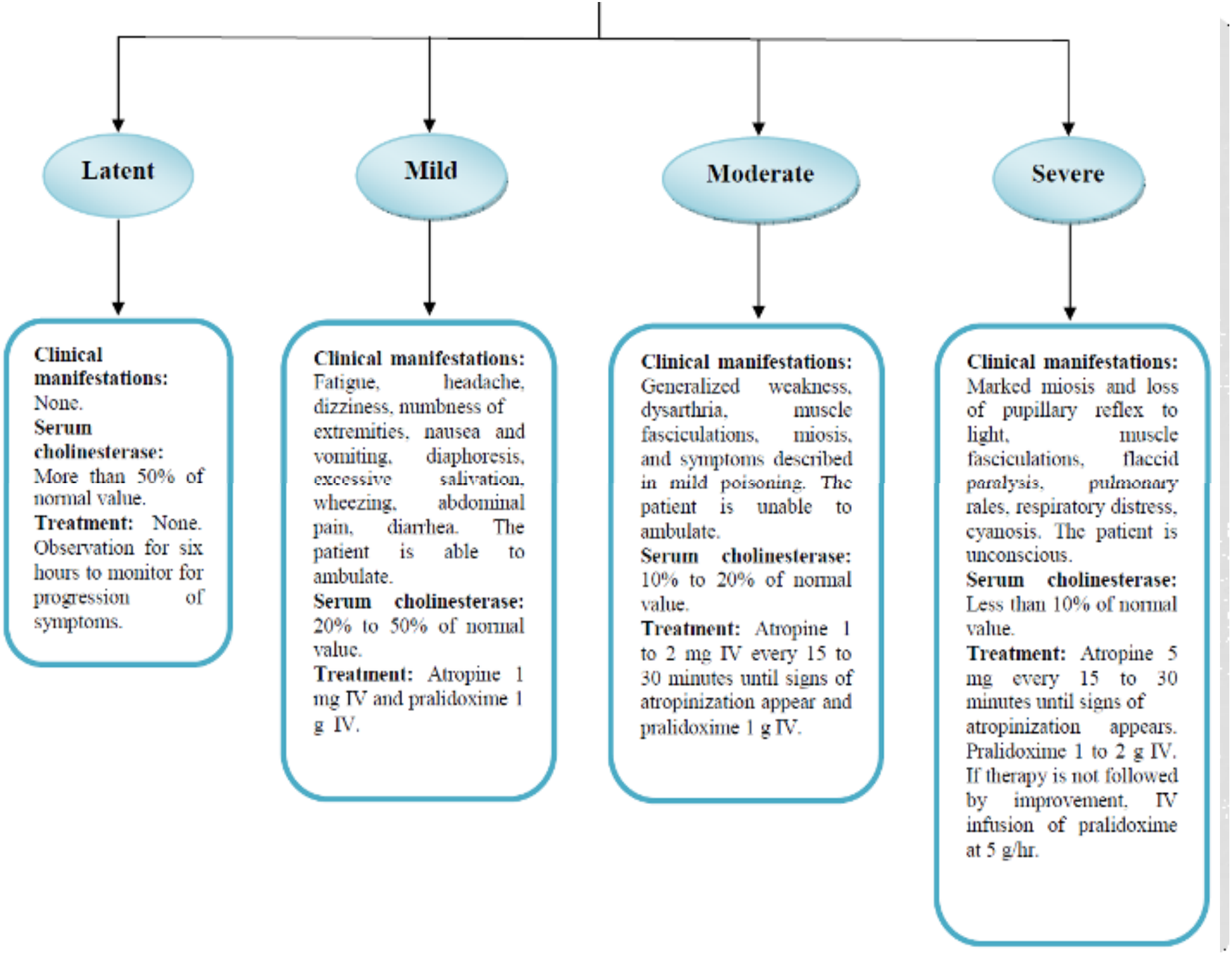
- **Antiglutamatergic** compound that was proved to be beneficial in conjunction with atropine, pralidoxime, and diazepam in nerve agents poisoning
- **Gacyclidine inhibited the neuropathology** that occurred 3 weeks following exposure in animals
- In **severe nerve agent poisoning**, gacyclidine can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

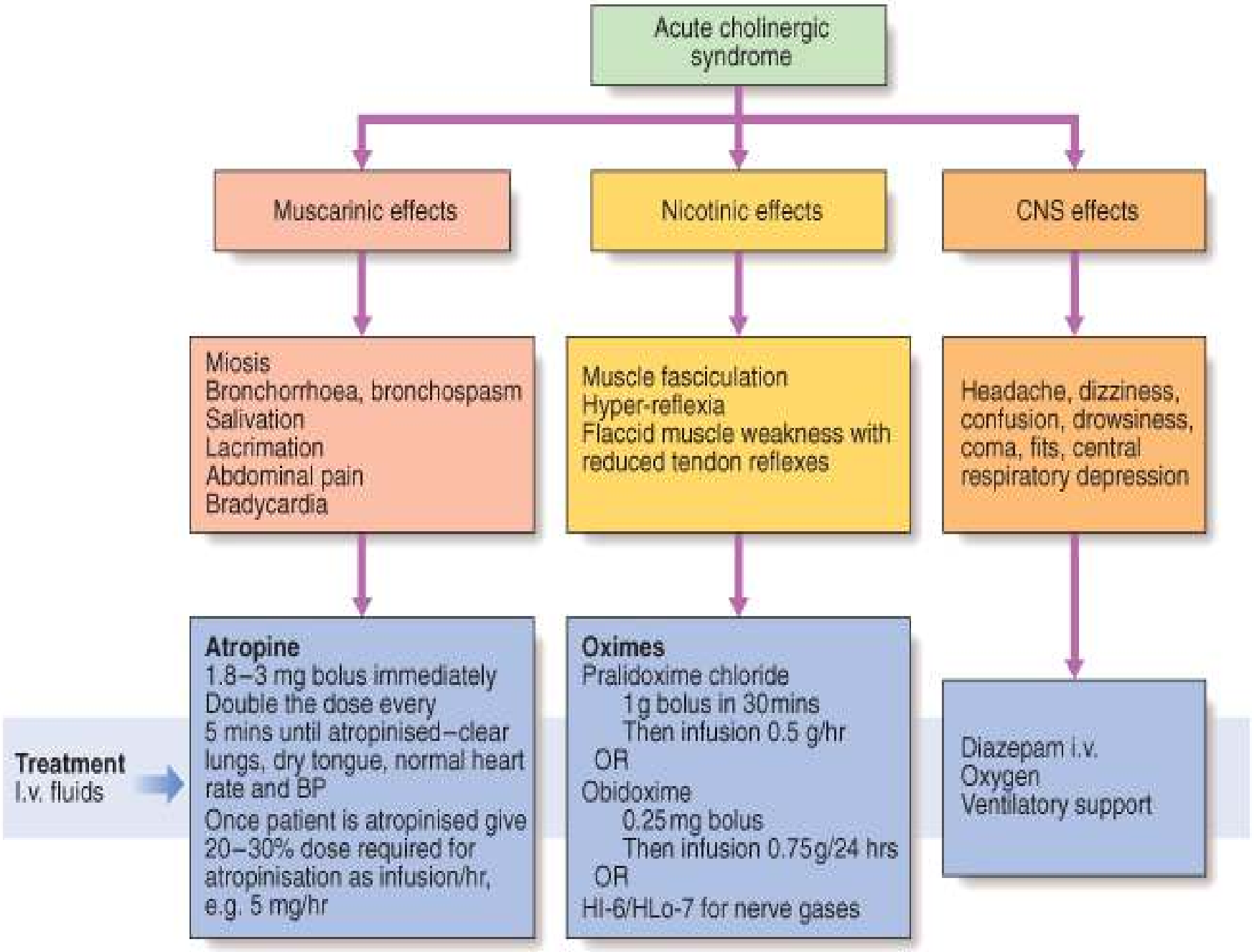
- Using hemodialysis, **hemoperfusion or hemofiltration is not clear.**

- 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


Latent
Mild
Moderate
Severe
Clinical manifestations: None.
Serum cholinesterase: More than 50% of normal value.
Treatment: None. Observation for six hours to monitor for progression of symptoms.
Clinical manifestations: Fatigue, headache, dizziness, numbness of extremities, nausea and vomiting, diaphoresis, excessive salivation, wheezing, abdominal pain, diarrhea. The patient is able to ambulate.
Serum cholinesterase: 20% to 50% of normal value.
Treatment: Atropine 1 mg IV and pralidoxime 1 g IV.
Clinical manifestations: Generalized weakness, dysarthria, muscle fasciculations, miosis, and symptoms described in mild poisoning. The patient is unable to ambulate.
Serum cholinesterase: 10% to 20% of normal value.
Treatment: Atropine 1 to 2 mg IV every 15 to 30 minutes until signs of atropinization appear and pralidoxime 1 g IV.
Clinical manifestations: Marked miosis and loss of pupillary reflex to light, muscle fasciculations, flaccid paralysis, pulmonary rales, respiratory distress, cyanosis. The patient is unconscious.
Serum cholinesterase: Less than 10% of normal value.
Treatment: Atropine 5 mg every 15 to 30 minutes until signs of atropinization appears. Pralidoxime 1 to 2 g IV. If therapy is not followed by improvement, IV infusion of pralidoxime at 5 g/hr.



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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No evidence that oximes are a useful treatment for organophosphate pesticide poisoning

Published:
16 February 2011

Authors:
Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J

Primary Review Group:
Injuries Group

Many thousands of people die every year because of poisoning by organophosphate pesticides. Most of the deaths are in developing countries. Drugs known as oximes are used as part of the standard recommended treatment, even though many doctors have said that they don't seem to have any benefit. This research has produced mixed evidence. Many of the studies had substantial limitations. Generally, the studies done to date do not support the routine use of oximes, however, they cannot exclude that there would be some doses or situations where a benefit would occur. The reviewers found that not enough research has been done to see whether oximes are actually effective or to define the doses that are more likely to be helpful. More research is needed before any firm conclusions can be drawn.

Authors' conclusions:

Current evidence is insufficient to indicate whether oximes are harmful or beneficial. The WHO recommended regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hr infusion) is not supported. Further RCTs are required to examine other strategies and regimens. There are many theoretical and practical reasons why oximes may not be useful, particularly for late presentations of dimethyl OP and those with a large excess of OP that simply re-inhibits reactivated enzymes. Future studies should screen for patient sub-groups that may benefit and may need flexible dosing strategies as clinical effectiveness and doses may depend on the type of OP.