Pesticides

Dr Kamal Hadidi

Applied to produce a more pleasant environment and abundant crops, man has developed and produced a variety of toxic chemicals.

Chemicals have been used **to kill or control unwanted pests**

Ideally pesticides should be highly selective, destroying target organisms while leaving non target organisms unharmed.

In reality, most pesticides are not so selective. “the benefits must be weighed against the risk”

BENEFITS ?

1. CONTROL OF VECTOR-BORNE DISEASES

2. INCREASED AGRICULTURAL PRODUCTIVITY

3. CONTROL OF URBAN PESTS.

RISKS?

ENVIRONMENTAL CONTAMINATION, “ENTER BOTH FOOD CHAINS AND NATURAL WATER SYSTEMS OR BIOACCUMULATION”

- *Classification*: Pesticides are often grouped by the pest they control (e.g. insecticides, rodenticides, fungicides, etc.) or categorized by chemical structure (e.g. insecticides are categorized as organophosphate, carbamate, organochlorine, synthetic-pyrethroid, and microbial and insect growth regulators). WHO classifies pesticides by hazards they pose based on Globally Harmonized System (GHS) from Category 1 (LD_{50} < 5 mg/kg body wt) to Category 5 (LD_{50} 2000–5000 mg/kg body wt) as given in **Table 58.1**.

Table 58.1: Classification of pesticides based on hazard

WHO Class		*Oral LD_{50}* (mg/kg body weight)*
Ia	Extremely hazardous	< 5
Ib	Highly hazardous	5–50
II	Moderately hazardous	50–2000
III	Slightly hazardous	> 2000
U	Unlikely to present acute hazard	> 5000

* LD_{50} value is a statistical estimate of the number of mg of toxicant per kg of body weight required to kill 50% of a large population of test animals: the rat is used unless otherwise stated.

Another method of classification of insecticides is based on their *mode of penetration*, i.e. whether they cause effect upon ingestion (stomach poisons), penetration of the body covering (contact poisons) or inhalation (fumigants).

- **Stomach poisons** are toxic only if ingested through the mouth and are useful against those insects that have biting or chewing mouth parts, such as caterpillars and grasshoppers, e.g. arsenicals like copper acetoarsenite (Paris green), calcium arsenate and lead arsenate; and fluorine compounds like NaF and cryolite.[1]
- **Contact poisons** penetrate the skin of the pest and are used against those arthropods that pierce the surface of a plant and suck out the juices. These can be divided into two groups: naturally occurring (nicotine, pyrethrum, rotenone and oils) and synthetic organic insecticides.[1] The main synthetic groups are the organic phosphates (organophosphates), carbamates and chlorinated hydrocarbons.
- **Fumigants** are toxic compounds that enter the respiratory system of the insect through its spiracles or breathing openings, e.g. HCN, naphthalene, methyl bromide and nicotine.

Most synthetic organic insecticides penetrate by all three of these pathways.

What's the difference?

pesticides

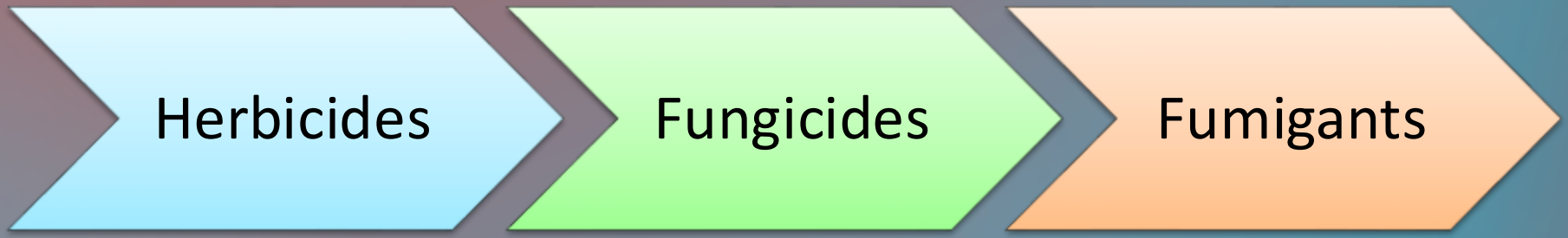
rodelentesides

Insectecides

Pesticides: Compounds that are used to kill pests.

Insecticides: Compounds that are used to kill insects and related species (e.g., organophosphates, organochlorines, carbamates).

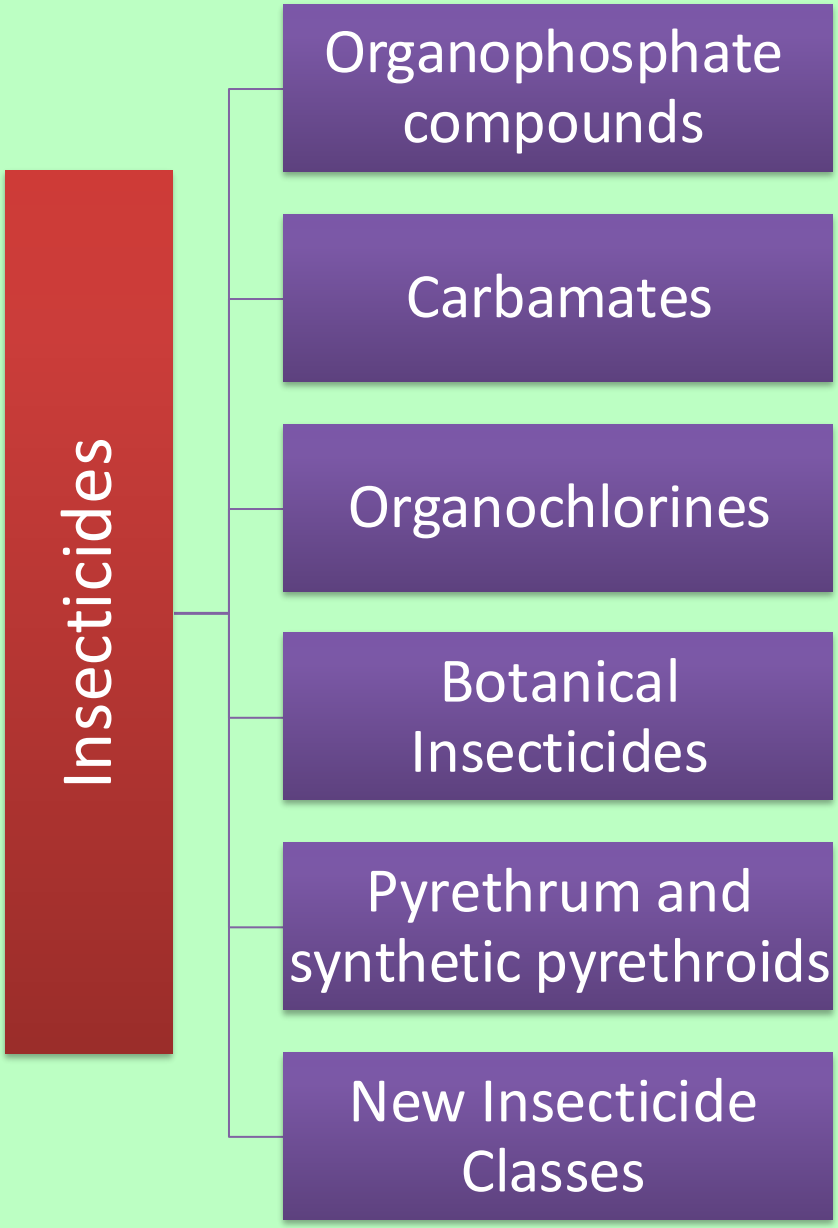
Rodenticides: Compounds that are used to kill rats,, mice, moles, and other rodents (e.g. anticoagulants, thallium, Vacor).


Herbicides
Fungicides
Fumigants

Herbicides: Compounds that are used to kill weeds (e.g., paraquat, diquat, [2,4-dichlorophenoxyjacetic acid [2,4-D]).

Fungicides: Compounds that are used to kill fungi and molds (e.g., dithiocarbamates, Captan).

Fumigants: Gases that are used to sterilize products (e.g., ethylene dibromide, methyl bromide).


Insecticides
Organophosphate compounds
Carbamates
Organochlorines
Botanical Insecticides
Pyrethrum and synthetic pyrethroids
New Insecticide Classes

PATHOPHYSIOLOGY

Organophosphates complex with the acetylcholinesterase enzymes

phosphorylation and deactivation

accumulation of large amounts of acetylcholine causes initial stimulation

exhaustion of cholinergic synapses

- Hydrolysis of the phosphorylated enzyme is slow and clinically unimportant

permanent deactivation

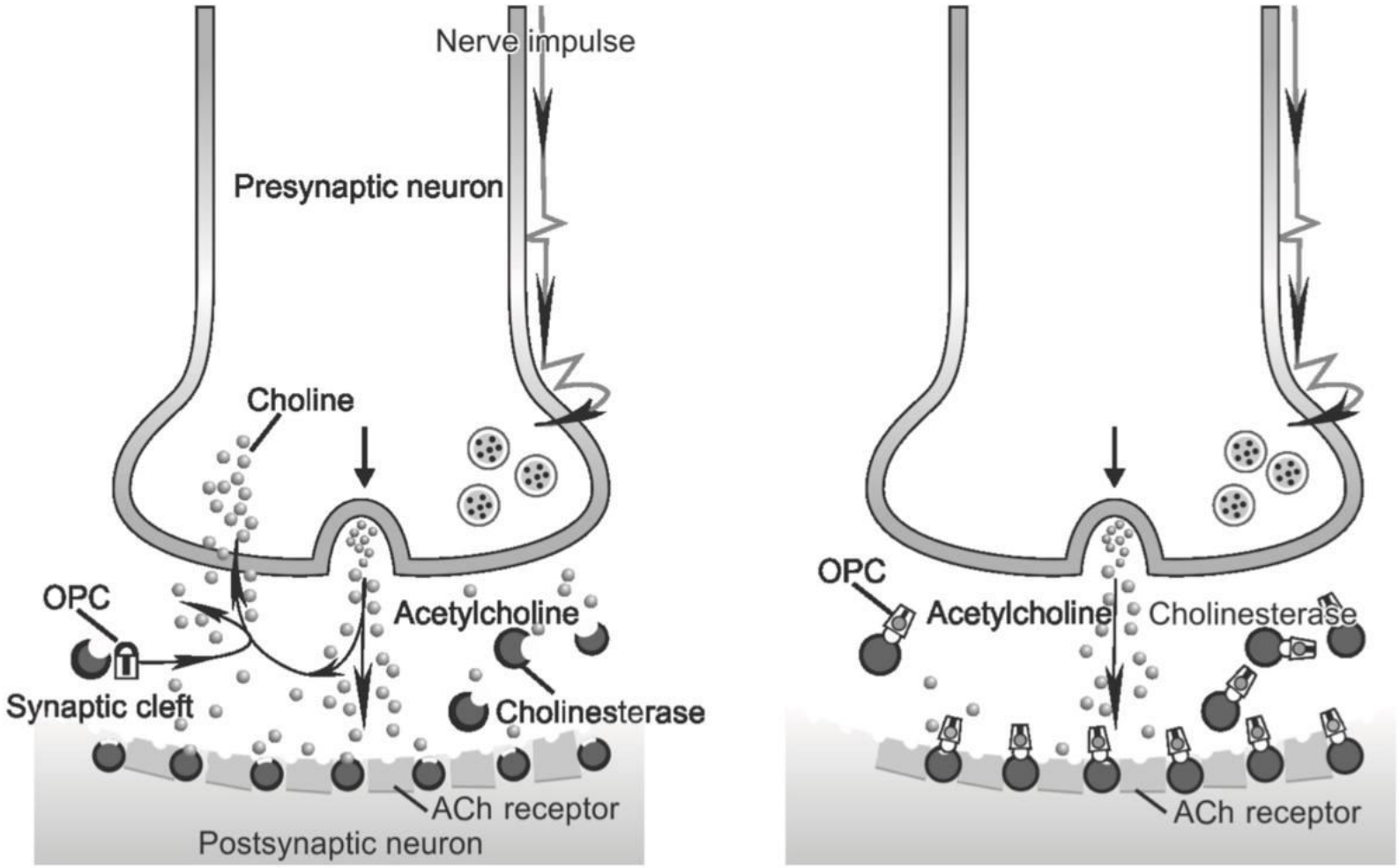


Fig. 58.2: OPCs 'lock' the AChE enzyme which prevents it to break acetylcholine

Clinical effects

Muscarinic effects: intestinal, bronchial, and bladder smooth muscle contraction, pupillary constriction and decreased reactivity, secretory gland stimulation, slowing of the sinus node and atrioventricular conduction, and ventricular dysrhythmias.

Nicotinic effects: persistent depolarization of skeletal muscles.

Central nervous system effects: causing initial stimulation and eventually depression of all activity and coma.

Organophosphorus Compounds (OPCs)

Fig. 58.1: OPC and carbamate

Absorption: OPCs and carbamates are absorbed by many routes including transdermal, transconjunctival, inhalational, across the GIT and through direct injection.

Metabolism: Most OPCs are hydrolyzed by enzymes, the A esterases or paroxonases which are not inhibited by it. These enzymes are found in the plasma and in the hepatic endoplasmic reticulum. The metabolic products are then excreted in the urine.

Delayed neurotoxicity

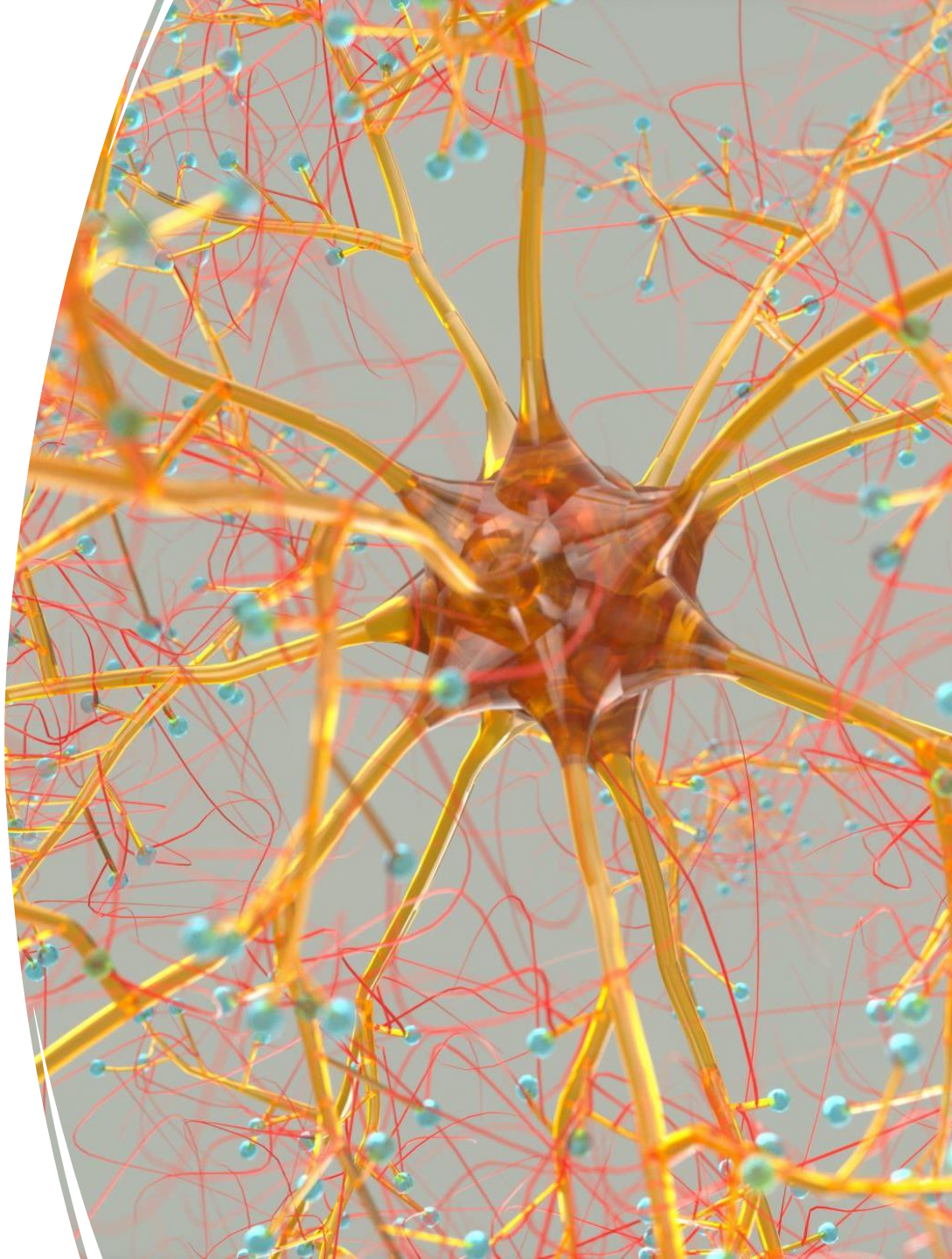
The histopathological lesion of organophosphorus ester induced delayed neurotoxicity is a Wallerian degeneration or "dying back" of axons rather than demyelination.

The process begins as a focal lesion, primarily in large myelinated fibers, and leads to axon death distal to the lesion.

Due to inhibition of “neurotoxic esterase “

Central Nervous System

- Anxiety
- Restlessness
- Tension
- Headache
- Ataxia
- Generalized weakness
- Convulsions
- Depression of respiratory => cyanosis



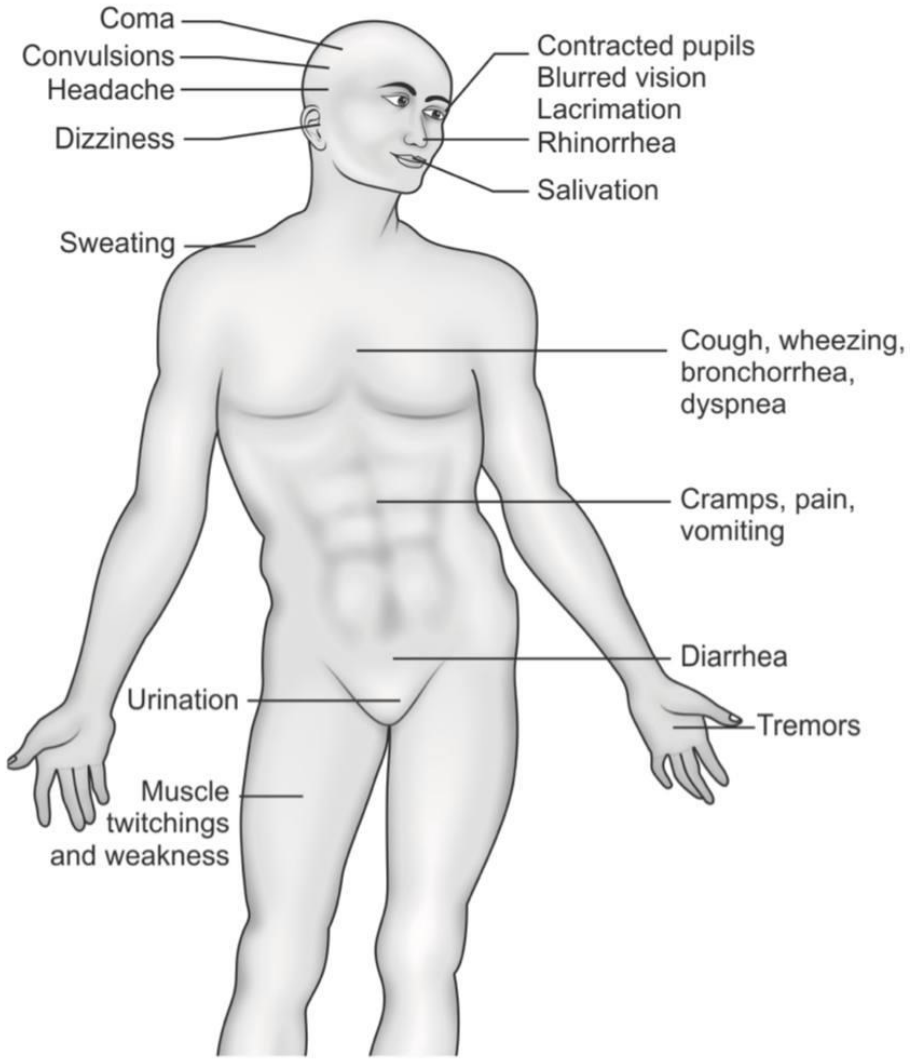


Fig. 58.3: Signs and symptoms of OPC poisoning

Table 58.2: Signs and symptoms depending on exposure		
Mild exposure	*Moderate exposure*	*Severe exposure*
• *GIT:* Nausea, anorexia, cramping	• SLUDGE	• SLUDGE
• *CNS:* Fatigue, headache, dizziness, tremors of tongue and eyelids, anxiety	• *CNS*: Anxiety, confusion, lethargy, incoordination	• *CNS*: Convulsions, coma, loss of sphincter tone, paralysis, autonomic dysfunction
• *MS:* Minimal muscle weakness	• *RS*: Respiratory muscle weakness	• *RS*: Insufficiency, pulmonary edema
• *Ocular:* Miosis, decreased visual acuity	• *MS*: Tremors, muscle fasciculations, followed by flaccid paralysis	• *CVS*: Bradycardia, heart block

Complications

Immediate	*Delayed*
• Pulmonary edema	• Paralysis[10]
• Aspiration pneumonia	• Neurotoxicity
• Chemical peritonitis	• Guillain-Barre syndrome
• Hyper-/hypoglycemia	
• Coagulation abnormalities	

Onset:

several hours post exposure, but symptoms can occur 5 minutes after massive ingestions.

The duration of illness:

depends on the severity of poisoning

Resolve:

by 1 month (mild to moderate organophosphate poisoning).

Presentations

Oder: garlic like odor emanating from the patient helps in diagnosis "maybe masked by the organic solvent"

Immune complex nephropathy with renal dysfunction and massive proteinuria occurred several weeks after a malathion exposure

Lungs: noncardiogenic pulmonary edema.

Skin: Can cause dermal irritation , but most are weak sensitizers

Chronic Effects

- *Polyneuropathy:*
- Paresthesias
- Weakness
- Easy fatigability
- Muscle cramps begin symmetrically in the distal lower extremities
- Improvement occurs over months to years, but some residual impairment usually remains

Neurobehavioral:

- Persistent neurological and behavioral abnormalities attributed to organophosphate exposure include:
  - drowsiness
  - mental confusion
  - anxiety
  - emotional liability
  - depression
  - fatigue
  - irritability
- most of the persistent symptoms that develop after acute organophosphate exposure resolve within 1yean

Diagnosis

A final diagnosis is rarely justified unless all of the following five conditions are present:

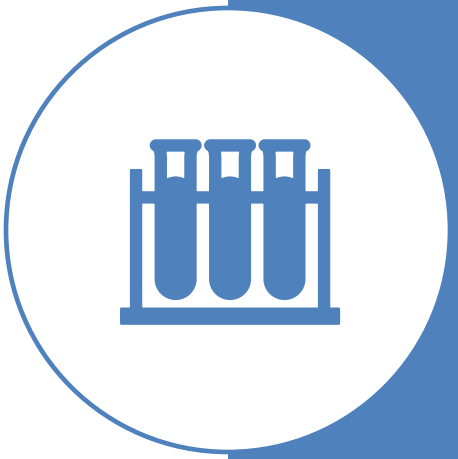
1) Definite history of exposure to OP
2) Latent interval of not more than a few hours between the last exposure and the onset of illness.

Diagnosis

3) Clinical picture in which most or all of the following signs or symptoms are present: headache./blurred vision/weakness. excessive perspiration/nausea /abdominal cramps/tightness in chest/and constricted pupils.
4) Reduction of plasma and RBC cholinesterase activity to a level substantially below 50% of baseline values.

LABORATORY LEVELS

- **Red Blood Cell Cholinesterase**
  - Inhibition of acetyl cholinesterase is a confirmatory test for organophosphate poisoning but is not diagnostic when used alone.
  - Blood cholinesterase level is the preferred index of toxic exposure, because it measures the same enzyme active in nervous tissue and less liable than the plasma cholinesterase level.



Stabilization

Manage respiratory problems resulting from weakness of respiratory muscles, central depression of respiration, bronchospasm, bronchial secretions, and pulmonary edema, which all result in hypoxemia.

Endotracheal intubation and assisted ventilation necessary to maintain adequate oxygenation.

Monitor PO2 carefully with arterial blood gases

Decontamination

Most of organophosphate insecticides contain hydrocarbon solvents, which have aspiration hazards.

Remove contaminated clothing.

Wash contaminated skin with water and then mild soap.

Atropine

- Atropine antagonizes both muscarinic and CNS effects of organophosphate poisoning
- Has no effect on muscle weakness or respiratory failure in severe poisoning, since this drug does not reactivate the cholinesterase enzymes
- For diagnosis => IV 1mg and watch signs within 10 min
- For therapy => IV 2-4mg/15min as needed
- Seriously poisoned patient may develop marked resistance to the usual doses of atropine

Pralidoxime

Specific "effectively reverses phosphorylation of the cholinesterase when given within 24hrs and up to 36-48 hours post exposure.

Ameliorates muscle weakness, fasciculation, and alterations of consciousness.

It does not relieve bronchospasm

Must be given concurrently with adequate atropine doses

Supportive Care

Avoid parasympathomimetic agents (physostigmine, succinylcholine) because they may potentiate anticholines-terase activity.

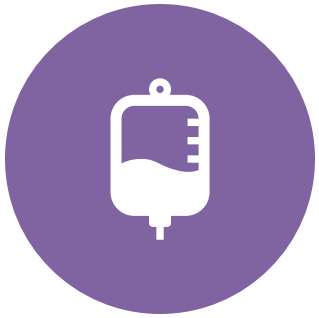
Phenothiazines and antihistamines have anticholinesterase activity and may potentiate organophosphate toxicity.

Central nervous system depressants (e.g., opiates) may increase the likelihood of respiratory arrest.

Supportive Care

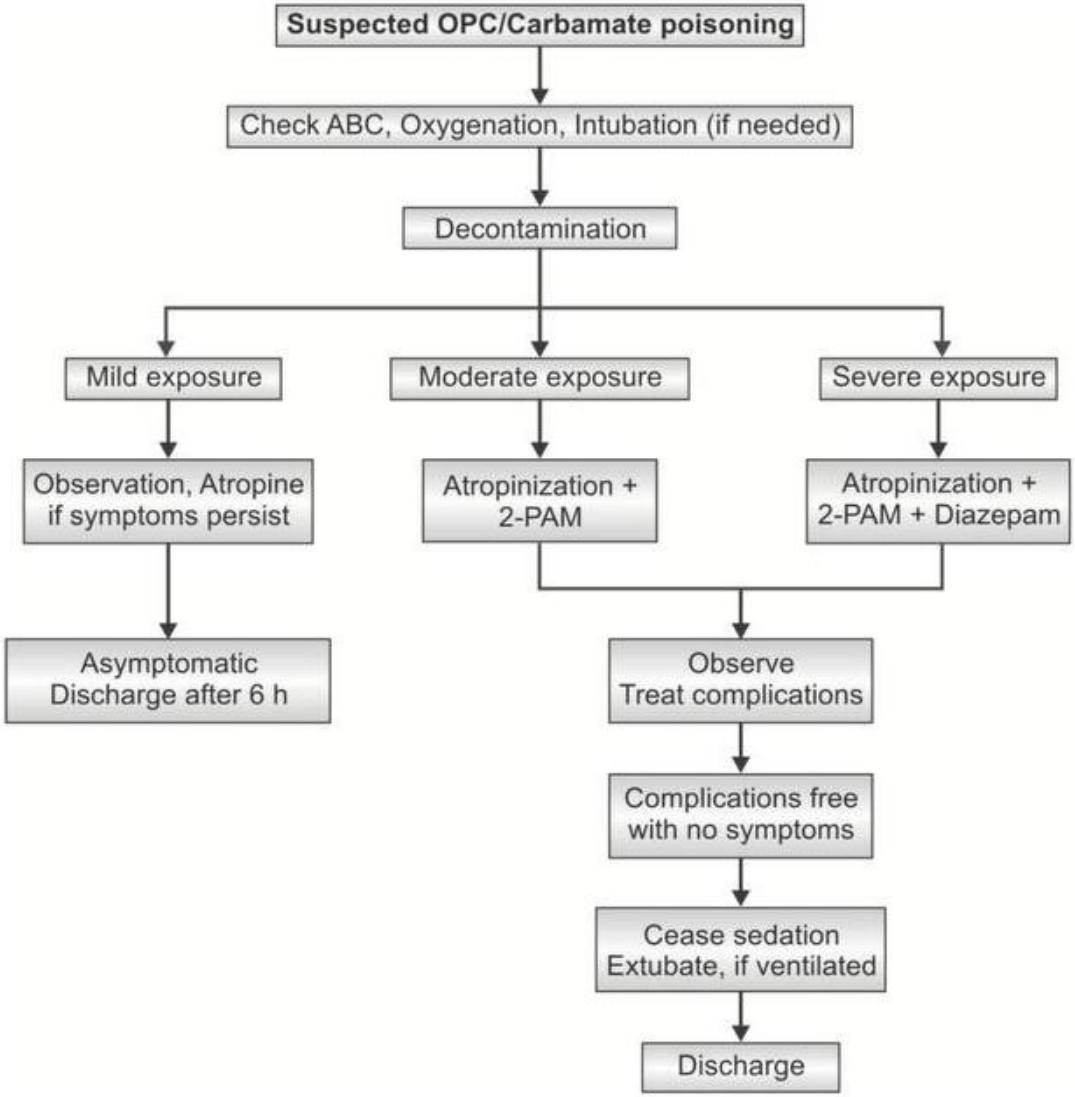
DURING ANTIDOTE ADMINISTRATION, THE PATIENT SHOULD BE FOLLOWED CLOSELY FOR SIGNS OF RESPIRATORY FAILURE AND ATROPINIZATION IN AN INTENSIVE CARE SETTING.

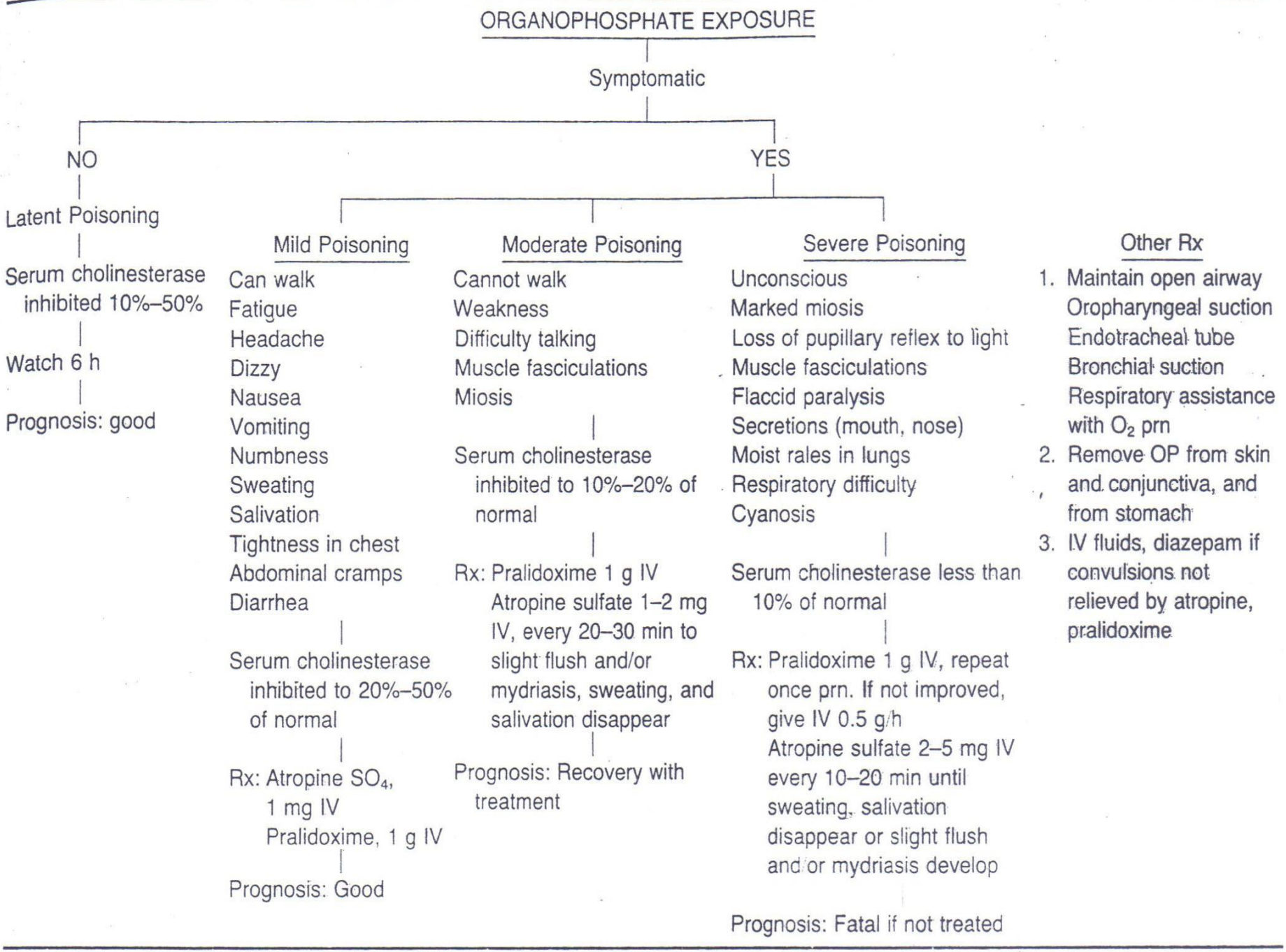
PATIENT SHOULD BE OBSERVED AT LEAST 48 HOURS AFTER THE LAST DOSE OF ATROPINE.



ADMINISTER FLUIDS ONLY TO REPLACE LOSSES.

Flow chart 58.1: Management of OPC poisoning





Adapted from Namba T, Nolte CT, Jarkrel J, et al: Poisoning due to organophosphate insecticides. Am J Med 1971;50:481. Used with permission.

Postmortem Findings

External

i. Kerosene-like smell from nostrils and mouth.
ii. Cyanosis of lips, fingers and nose.
iii. Deep postmortem staining.
iv. Congested face.
v. Frothy discharge, often bloodstained from the nose and mouth.

Internal

i. Mucosa of the stomach and intestine is congested.
ii. Stomach content may give kerosene-like smell.

iii. Respiratory passages are congested, contain frothy hemorrhagic exudates.
iv. Petechial hemorrhage may be present subpleurally.
v. Edema and congestion of the lungs and other visceral organs.
vi. Edema of brain.

- Suicidal poisoning is common in our country, both in rural and urban areas. OPCs are also common suicidal agents in Pakistan, Sri Lanka and the other Asian and South East Asian countries.
- Homicidal poisoning does not occur due to detectable smell of the diluents, and signs and symptoms appear rather early.

CARBAMATES

- Produces a clinical picture of cholinesterase inhibitors similar to OP toxicity with several exceptions :
  - In vivo spontaneous hydrolysis of carbamelyated cholinoestrase enzyme leading to less sever shorter duration of symptoms
  - Carbamate poorly penetrate the BBB, producing minimal CNS effects

Treatment

- Management approach is similar to that for organophosphate poisoning

- **Pralidoxime usually is not recommended**
- May increase acetylchiolinesterase activation

Antidotes

- Atropine is the antidote of choice as in organophosphate poisoning.
- Although the total amount of atropine required usually is less, the same initial doses are recommended
- Patients require approximately 6-12 hours of atropine treatment, but all significantly poisoned patients should be observed at least 24 hours after the last atropine dose

ORGANOCHLORINES

Most organochlorine pesticide compounds have been replaced by organophosphates.

The EPA banned many organochlorine compounds (e.g., DDT, endrin) because these products are stored indefinitely in human tissue.

Lindane is the most common OC as a garden spray

Methoxychlor ,kethane are also available

The use of OC is severely restricted

PHARMACOKINETICS

Organochlorines are well absorbed from the lungs, gastrointestinal tract, and skin.

Serious toxicity occurs after ingestion of lindane dissolved in organic solvents but **less than 0.1% of an ingested dose** of lindane pellets **appears in the blood.**

Topically, **approximately 10% of the applied dose is absorbed**, but lipid solvents increase dermal penetration.

Most organochlorines are metabolized slowly and are **excreted primarily in the feces.**

Central Nervous System

ORGANOCHLORINES ARE CNS STIMULATORS THAT PRODUCE APPREHENSION, EXCITABILITY, PARESTHESIAS, DIZZINESS, HEADACHE, DIS- ORIENTATION, AND TREMOR PROGRESSING TO STUPOR, COMA, AND CONVULSIONS IN SEVERE CASES.

ORGANOCHLORINES MAY ENHANCE MYOCARDIAL IRRITABILITY, LEADING TO CARDIAC DYSRHYTHMIAS AFTER HEAVY EXPOSURES.

SERIOUS COMPLICATIONS INVOLVE SEIZURES WITH RESULTANT HYPOXEMIA, SEVERE METABOLIC ACIDOSIS, AND DEATH.

Stabilization

Seizures, hypoxemia, and resultant acidosis are the immediate life threatening emergencies.

Diazepam is the anticonvulsant of choice.

Moderately to severely poisoned patients should have intravenous lines and a cardiac monitor.

Decontamination

MOST OC INSECTICIDES CONTAIN ORGANIC SOLVENTS, WHICH ARE SEVERE ASPIRATION HAZARDS.

SKIN DECONTAMINATION (REMOVAL OF CONTAMINATED CLOTHES, WASHING OF AREA WITH WATER AND GREEN OR MILD SOAP) IS NECESSARY TO PREVENT CONTINUED DERMAL ABSORPTION.


Thank You