# Pesticides

## Insecticides

Dr. Kamal Hadidi,
Professor of Toxicology
School of Medicine
The University of Jordan

# Pesticides

- 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”
- Among the benefits of pesticides are control of vector-borne diseases, increased agricultural productivity, and control of urban pests.
- A major risk is environmental contamination, “enter both food chains and natural water systems or bioaccumulation”

# Definitions

- *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:* 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, leading to phosphorylation and deactivation.
- The resultant accumulation of large amounts of acetylcholine causes initial stimulation, then exhaustion of cholinergic synapses.
- Hydrolysis of the phosphorylated enzyme is slow and clinically unimportant, resulting in permanent deactivation.

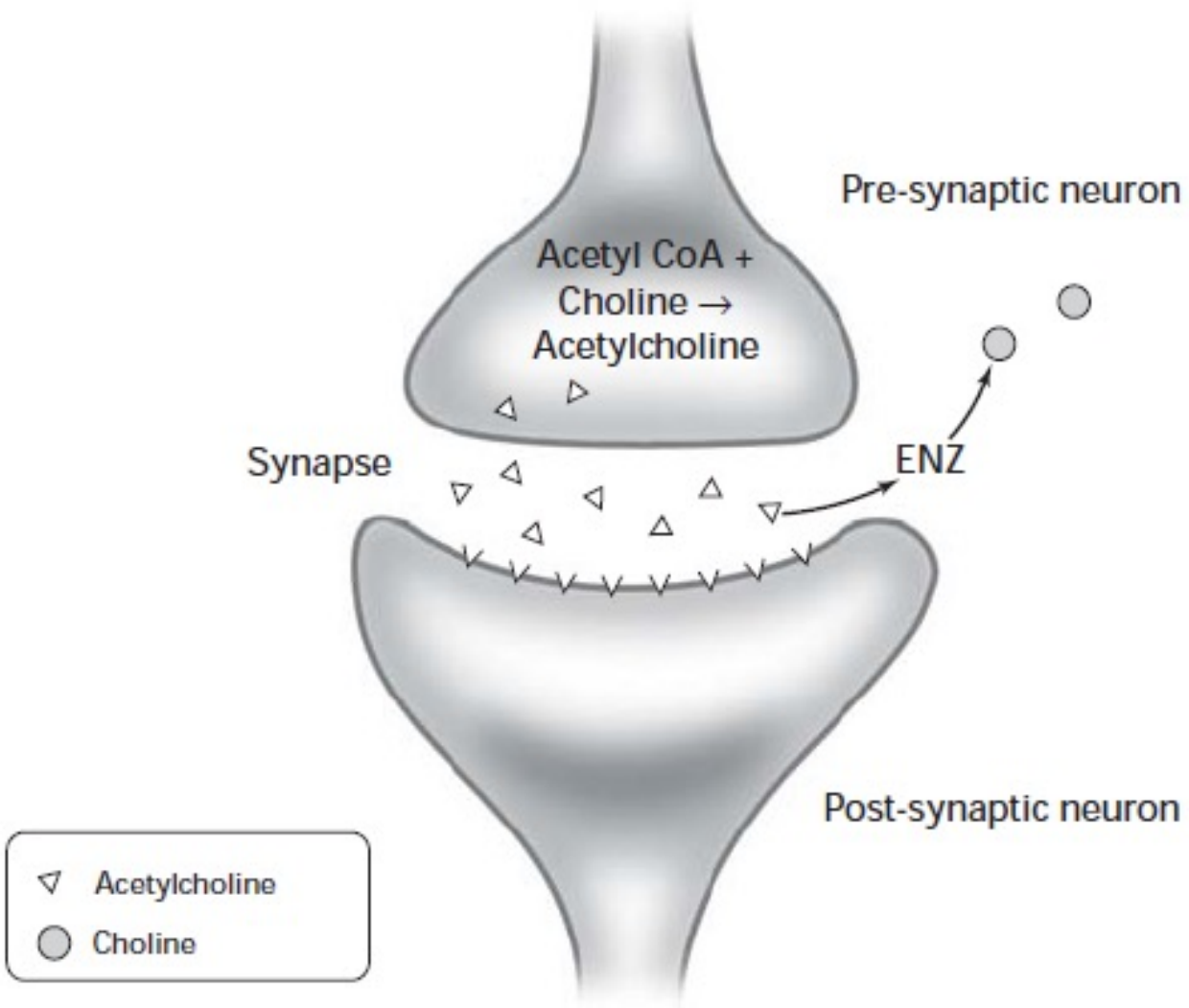


**FIGURE 17.4** Chemistry at the cholinergic synapse. ACh = acetylcholine, ACE = acetylcholinesterase, X = postsynaptic receptor.

# 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.

# 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

# symptoms

- Symptoms develop several hours post exposure, but symptoms can occur 5 minutes after massive ingestions.
- The duration of illness depends on the severity of poisoning, since several months may be required for cholinesterase activity to return to normal levels.
- Symptoms of mild to moderate organophosphate poisoning usually resolve by 1 month.

# Presentations

- Oder: garlic like odor emanating from the patient helps in diagnosis “maybe masked by the organic solvent”
- Skin: Can cause dermal irritation , but most are weak sensitizers
- Lungs: noncardiogenic pulmonary edema.
- Immune complex nephropathy with renal dysfunction and massive proteinuria occurred several weeks after a malathion exposure.

# Chronic Effects

- *Polyneuropathy:* Paresthesias, weakness, easy fatigability, and 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, and 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 measure the same enzyme active in nervous tissue and is 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.

# ORGANOPHOSPHATE EXPOSURE

Symptomatic

## NO

Latent Poisoning

Serum cholinesterase inhibited 10%–50%

Watch 6 h

Prognosis: good

## YES

### Mild Poisoning

Can walk
Fatigue
Headache
Dizzy
Nausea
Vomiting
Numbness
Sweating
Salivation
Tightness in chest
Abdominal cramps
Diarrhea

Serum cholinesterase inhibited to 20%–50% of normal

Rx: Atropine $SO_4$, 1 mg IV
Pralidoxime, 1 g IV

Prognosis: Good

### Moderate Poisoning

Cannot walk
Weakness
Difficulty talking
Muscle fasciculations
Miosis

Serum cholinesterase inhibited to 10%–20% of normal

Rx: Pralidoxime 1 g IV
Atropine sulfate 1–2 mg IV, every 20–30 min to slight flush and/or mydriasis, sweating, and salivation disappear

Prognosis: Recovery with treatment

### Severe Poisoning

Unconscious
Marked miosis
Loss of pupillary reflex to light
Muscle fasciculations
Flaccid paralysis
Secretions (mouth, nose)
Moist rales in lungs
Respiratory difficulty
Cyanosis

Serum cholinesterase less than 10% of normal

Rx: Pralidoxime 1 g IV, repeat once prn. If not improved, give IV 0.5 g/h
Atropine sulfate 2–5 mg IV every 10–20 min until sweating, salivation disappear or slight flush and/or mydriasis develop

Prognosis: Fatal if not treated

### Other Rx

1. Maintain open airway
   Oropharyngeal suction
   Endotracheal tube
   Bronchial suction
   Respiratory assistance with $O_2$ prn
2. Remove OP from skin and conjunctiva, and from stomach
3. IV fluids, diazepam if convulsions not relieved by atropine, pralidoxime

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

# 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.