ORGANOPHOSPHORUS COMPOUND POISONING

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INTRODUCTION

Organophosphorus (OP) compounds are widely used as pesticides, especially in developing countries. The case fatality rate following deliberate ingestion of OP pesticides in developing countries in Asia is 5–20%.

- **Intrduction:** Organophosphorus (OP) compounds are widely used as pesticides, common cause of poisoning in the developing world.
- A global public health problem especially in developing countries.
- Organophosphate poisoning occurs most commonly as a suicide attempt in farming areas of the developing world and less commonly by accident.
- The case fatality rate following deliberate ingestion of OP pesticides in developing countries in Asia is 5–20%.

Organophosphorus compounds

Nerve agents :

- G agents: sarin, tabun,soman
- V agents: VX,VE

Insecticides :

Dimethyl compounds	Diethyl compounds
Dichlorvos	Chlorpyrifos
Malathion	Diazinon
Fenthion	Parathion-ethayl
Methamidophos	Quinalphos

MECHANISM OF TOXICITY

OP compounds phosphonylate the active site of acetylcholinesterase(AChE), inactivating the enzyme and leading to the accumulation of acetylcholine (ACh) in cholinergic synapses. Spontaneous hydrolysis of the OP–enzyme complex allows reactivation of the enzyme. However, loss of a chemical group from the OP–enzyme complex prevents further enzyme reactivation, a process termed ‘ageing’.

CONTD…

After ageing has been taken place, new enzyme needs to be synthesised before function can be restored. The rate of ageing is more rapid with dimethyl compound (3.7 hours) than diethyl (31 hours), and especialy rapid with nerve agents (within minutes).

In addition, plasma cholinesterase (also called butylcholinesterase [BuChE] or pseudocholinesterase) and neuropathy target esterase (NTE) are inhibited by organophosphorus agents.

CLINICAL FEATURES

- Four clinical syndroms have been described :

1. Acute cholinergic syndrome
2. Intermediate syndrome (IMS)
3. Organophosphate induced delayed polyneuropathy (OPIDN)
4. Chronic organophosphate induced neuropsychiatric disorder (COPIND)

CONTD…

Onset and duration of AChE inhibition varies depending on the organophosphorus agent's rate of AChE inhibition, the route of absorption, enzymatic conversion to active metabolites, and the lipophilicity of the organophosphorus agent. For most agents, oral or respiratory exposures generally result in signs or symptoms within three hours, while symptoms of toxicity from dermal absorption may be delayed up to 12 hours.

CONTD…

- Lipophilic agents such as dichlofenthion, fenthion, and malathion are associated with delayed onset of symptoms (up to five days) and prolonged illness (greater than 30 days), which may be related to rapid adipose fat uptake and delayed redistribution from the fat stores.

ACUTE CHOLINERGIC SYNDROME

MUSCARININC FEATURES (*DUMBBELSS*)

- D iarrhoea
- U rination
- M iosis
- B ronchorrhea
- B ronchospasm
- E mesis
- L acrimation
- S alivation
- S weating

CONTD…

NICOTINIC FEATURES

- Muscle weakness
- Muscle fasiculations
- Muscle paralysis
- Hypertension
- Tachycardia

CONTD…

CNS FEATURES

- Fatigue
- Confusion
- Unconsciousness
- Seizues
- Ataxia
- Resp. depression

INTERMEDIATE SYNDROME (IMS)

- Occurs 1-4 days after resolution of acute cholinergic crisis and may last 2-3 weeks
- Incidence = 10-50 %
- May occur from inadequate oxime therapy
- Prolonged effects on Nicotinic receptors
- Primary motor end plate degeneration
- Leads to muscle weakness

CONTD…

IMS- muscle weakness of

- Muscles innervated by cranial nerves : III-VII and X
- Neck flexors
  - a constant feature
  - one of the earliest signs
  - inability of patients to raise heads off pillow
- Proximal limb muscle weakness
  - typically involve shoulder abductors, hip flexors
- Respiratory muscles - paralysis

CONTD…

- Deep tendon Reflexes :

  Usually absent / decreased

- Sensory system usually intact
- Muscarinic symptoms :

  absent

  rarely short relapses may occur

ORGANOPHOSPHORUS INDUCED DELAYED POLYNEUROPATHY (OPIDN)

- Delayed, rare, neurotoxic effect
- Occurs 2-3 weeks after severe acute poisoning, due to slow release of OP from body fat
- Neuropathy target esterase (NTE) are inhibited by organophosphorus compounds
- symmetrical sensory-motor axonal degeneration of the peripheral nerves and SC

CONTD…

Motor

1. Sharp cramp like pain in calf
2. High stepping gait (initially)
3. Shuffling gate in severe cases
4. Quadriplegia / paraplegia
5. Wrist and foot drop
6. Mild pyramidal signs

Sensory

1. Glove-stocking anesthesia
2. Cerebellar signs +/-

CHRONIC OP INDUCED NEUROPSYCHIATRIC DISORDER (COPIND)

- Chronic low-dose exposure to OP compounds
- 40 hours/week, 9 months/ year
- No cholinergic symptoms
- Non responsive to levodopa
- Plasma cholinesterase levels are normal

CONTD…

Neurological Symptoms

1. Impairment in memory
2. Impairment in concentration
3. Impairment in leaning
4. Chronic fatigue
5. EPS : dystonia
6. Resting tremor, bradykinesia, rigidity, postural instability

Psychiatric Symptoms

1. Anxiety
2. Dysthymia
3. Depression

DIAGNOSIS

Diagnosis is mainly clinical, Based on :

1. H/o Ingestion of poison
2. Characteristic clinical features
3. Clinical improvement after atropine
4. Inhibition of cholinesterase activity

INVESTIGATIONS

- Routine laboratory tests :
  - complete blood count
  - Blood sugar
  - Liver function test
  - S. creatinine
  - S. electrolytes
  - S. amylase
  - ECG
  - Chest x-ray
  - Urine RME

INVESTIGATIONS

- Special test :
  - Direct measurement of OPC
  - Estimation of plasma and RBC cholinesterase
  - Estimation of neuropathic transferase enzyme
  - Electro-neuro-myogram (ENMG)

MANAGEMENT

1. Initial stabilization of patient by maintaining respiration and other vital signs
2. Reduction of exposure
3. Administration of specific antidote
4. Supportive treatment

ANTIDOTE

Two antidotes in the treatment of OPC poisoning :

- **Atropine** : is the antidote of choice which reverses the muscarinic features
- **Oxime** : which reactivate cholinesterases and reverses the nicotinic features

Atropine :

- Start with 1.8-3.0 mg fast iv bolus
- Double the dose of atropine every 5 minutes until signs of atropinisation appear

ATROPINE

Target Endpoints of Atropinization.

1. Drying of Pulmonary secretions, ie. Clear lung fields on auscultation. (Most reliable)
2. Heart rate > 80 beats / min.
3. SBP > 80 mmHg.
4. Pupils : No longer pinpoint.
5. Dry Axillae.

ATROPINE

Maintenance infusion

- once the patient is stable start an infusion of 5% dextrose containing 10-20% of the total initial dose of atropine on an hourly basis.

ATROPINE

- stop atropine infusion if features of toxicity appears :

  confusion, urinary retention, hyperthermia, bowel ileus, agitation, flushing, tachycardia
- Stop infusion for 30 min, if toxicity.
- Re-start infusion at 80% of initial rate, once the temperature comes down and patient calms.
- Most do not need >3-5 mg (5-9 ml) / hour of atropine infusion.
- Reduce rate by 20% every 4 hourly once patient is stable. STOP.

OXIMES

- Reactivate Acetyl cholinesterase, remove phosphoryl group.
- Among various oximes (obidoxime and trimedoxime) Pralidoxime (PAM) remains, most widely used.
- Prevent continued toxicity by Scavenging and detoxifying enzyme.
- Available in four Salts : chloride, iodide, metilsulfate, and mesilate.
- Chloride and iodide most widely used in developing countries.
- Chloride salt better than iodide.

OXIMES

Therapeutic effectiveness depends on

1. Concentration of poison consumed (Poison load).
2. Time lapse between poisoning and administration
3. Type of OPC. (More effective on diethyl than dimethyl). Dimethyl compound reactivate and “age” at slower rate.
4. Lipid solubility of OPC.
5. Concentration of Oxime in blood.
6. Treatment with oximes should be started as early as possible, no role if started after 48 hours and should not be preceded by atropine administration.

OXIMES

Pralidoxime :

- Give 30mg/kg loading dose IV over 10-20mins followed by continuous infusion of 8-10mg/kg/hr until clinical recovery.
- Infusion continued until patient remains symptom free for atleast 12 hours without additional atropine or until extubated.

SUPPORTIVE MANAGEMENT

- Management of respiratory insufficiency
- Maintenance of circulation
- Treatment of convulsion
- Fluid and electrolyte balance
- Control of infection
- Management of pulmonary oedema
- Mantenance of nutrition
- Control of body temperature

CAUSE OF DEATH IN OPC POISONING

- Respiratory failure
- Ventricular arrhythmia
- Torsades de points
- Seizures
- Pulmonary edema

ABSTRACT

- Acute toxicity from organophosphorus agents presents with manifestations of cholinergic excess. The dominant clinical features of acute cholinergic toxicity include bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, urination, emesis, and diarrhea.

- 10 - 50 percent of organophosphorus poisoned patients develop a distinct neurologic disorder 24 to 96 hours after exposure. This disorder consists of characteristic neurological findings including neck flexion weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency.
- The diagnosis of organophosphate (OP) poisoning is made on clinical grounds. In the absence of a known ingestion or exposure, the clinical features of cholinergic excess reflect the possibility of OP poisoning.

- Patients with markedly depressed mental status require 100 percent oxygen and immediate tracheal intubation. Furthermore, poisoned patients may rapidly develop respiratory failure.
- Introduce atropine therapy for all patients with any degree of possible cholinergic toxicity from OP.
- Oxime therapy (eg, pralidoxime) can be given to all patients with evidence of cholinergic toxicity, patients with neuromuscular dysfunction, or patients with exposures to organophosphorus agents known to cause delayed neurotoxicity . Pralidoxime should not be administered without concurrent atropine.

HAVE A GOOD DAY