

INTRODUCTION



- Organophosphorus compounds are **chemical** agents in wide-spread use throughout the world, mainly in **agriculture**.
- They are also used as **nerve agents** in chemical warfare (e.g. Sarin gas), and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma.
- They comprise the ester, amide or thiol derivatives of phosphoric acid and are most commonly used as **pesticides** in commercial agriculture, **field sprays** and as **household chemicals**.



- There are no rules and regulations governing the purchase of these products, and they are therefore readily available “over the counter”, despite them being a major cause of morbidity and mortality.
- Exposure to organophosphates in an attempt to commit suicide is a key problem, particularly in the developing countries, and is a more common cause of poisoning than the chronic exposure experienced by farmers or sprayers in contact with pesticides.

CLASSIFICATION



- There are more than a hundred organophosphorus compounds in common use. These are classified according to their toxicity and clinical use:
- 1. **Highly toxic organophosphates:** (e.g. tetra-ethyl pyrophosphates, parathion). These are mainly used as **agricultural insecticides**.
- 2. **Intermediately toxic organophosphates:** (e.g. coumaphos, clorpyrifos, trichlorfon). These are used as **animal insecticides**.
- 3. **Low toxicity:** (e.g. diazinon, malathion, dichlorvos). These are used for **household application and as field sprays**.

Types of organophosphate



Insecticides	Nerve gases	Antihelminthic agents	Herbicides
Malathion	Soman	Trichlorfon	Tribufos [DEF]
Parathion	Sarin		Merphos
Diazinon	Tabun		
Fenthion	VX		
Dichlorvos			
Chlorpyrifos			
Ethion			

Exposure



Home Exposure	Occupational Exposure	Other Exposure
Accidental ingestion	Farms & Farm worker	Dietary exposure- Pesticide residues on crops
Lawn and garden use	Pesticide applicator	Leaching from soils to ground water
Insect control	Manufacture	Community exposure
Food supply	Mixing and handling	Airborne drift from commercial app
Water supply	Landscapers	Contaminated drinking water

Absorption route



- Cutaneous
- Ingestion (Accidental Or Suicidal)
- Inhalation
- Injection

Pharmacokinetics



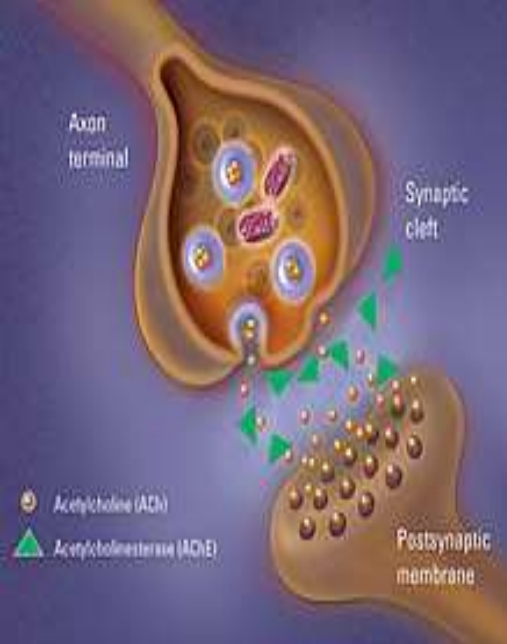
- Most organophosphates are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts.
- They are rapidly redistributed to all body tissues.
- The highest concentrations are found in the liver and kidneys.



- This high lipid solubility means that they easily cross the blood/brain barrier and therefore produce potent effects on the CNS.
- Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half-life of minutes - hours.



- The oxidative metabolites of malathion and parathion (malaoxon and paraoxon) are active forms and are subsequently hydrolyzed into inactive metabolites.
- Elimination of organophosphorus compounds and its metabolites occur mainly via urine, bile and faeces



mechanism of action

OP Inactivate Acetyl Cholinesterase (ACh E).
Establishment Of A Covalent Bond With AchE.

- ACh E Is An Enzyme That Degrades The Neurotransmitter Acetylcholine (ACh) Into Choline And Acetic Acid.
- ACh Is Found In CNS & PNS, Neuromuscular Junctions, And Red Blood Cells (RBCS).
- Once ACh E - Inactivated, **ACh Accumulates** Throughout The Nervous System → **Overstimulation Of Muscarinic And Nicotinic Receptors.**



Once an organophosphate binds to AChE, the enzyme can undergo one of the following:

- **Endogenous hydrolysis** of the phosphorylated enzyme by esterases or paraoxonases
- **Reactivation** by a strong nucleophile such as pralidoxime (2-PAM)
- **Irreversible binding** and permanent enzyme **inactivation (aging)**

The onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation

Clinical features of Organophosphorus Poisoning

- Following exposure to organophosphorus compounds, the toxic features are usually obvious within 30 minutes to 3 hours.
- This may be delayed in some cases depending on the rate and amount of systemic absorption.
- The majority of patients give a history of intentional or accidental ingestion of organophosphorus compounds.
- Toxicity is produced by the rapid absorption of the compound through the gastrointestinal, respiratory tracts and skin.

Cont...



- The clinical symptoms and signs are non-specific and will depend on the specific agent, the quantity and the route of entry.
- Some patients present with vomiting, diarrhoea and abdominal pain, whilst others may be unconscious on arrival at the hospital. A high index of suspicion is therefore needed to make an early diagnosis.
- The clinical features can be broadly classified as secondary to the
 - (a) muscarinic effects
 - (b) nicotinic effects and
 - (c) central receptor stimulation.



- Early cases present predominantly with parasympathetic over-activity, and a characteristic garlic smell.
- The end result may be a multi-system manifestation involving the gastrointestinal, respiratory, cardiovascular and nervous systems, as well as involvement of skeletal muscle, other organs and metabolic effects such as hypo- or hyperglycemia.
- Most fatalities occur within 24 hours and those who recover usually do so within 10 days.

Symptoms and signs

Muscarinic receptors	Nicotinic receptors	Central receptors
<p>Cardiovascular</p> <ul style="list-style-type: none">● Bradycardia● Hypotension <p>Respiratory</p> <ul style="list-style-type: none">● Rhinorrhoea● Bronchorrhoea● Bronchospasm● Cough <p>Gastrointestinal</p> <ul style="list-style-type: none">● Nausea/vomiting● Increased salivation● Abdominal cramps● Diarrhoea● Faecal incontinence <p>Genitourinary</p> <ul style="list-style-type: none">● Urinary continence <p>Eyes</p> <ul style="list-style-type: none">● Blurred vision● Increased lacrimation● Miosis <p>Glands</p> <ul style="list-style-type: none">● Excessive salivation	<p>Cardiovascular</p> <ul style="list-style-type: none">● Tachycardia● Hypertension <p>Musculoskeletal</p> <ul style="list-style-type: none">● Weakness● Fasciculations● Cramps● Paralysis	<p>General effects</p> <ul style="list-style-type: none">● Anxiety● Restlessness● Ataxia● Convulsions● Insomnia● Dysarthria● Tremors● Coma● Absent reflexes● Respiratory depression● Circulatory collapse

Who classification for severity



MILD	MODERATE	SEVERE
Serum/rbc cholinesterase level 2-8 u/l	0.8-2 u/l	<0.8 u/l
Walks and talks Abd pain nausea vomit headache Salivation sweating	Talks with soft voice Cannot walk Fasiculations present Miosis restlessness anxiety	Coma convulsions profuse bronchial secretions

Cardiac manifestations



- The commonest cardiac manifestations following poisoning are hypotension (with warm, dilated peripheries), and bradycardia. Patients seldom present with tachycardia and hypertension due to predominant nicotinic receptor stimulation.
- Cardiac manifestations are often the cause of serious complications and fatality.
- Electrocardiographic manifestations include **prolonged Q-Tc intervals, elevation of the ST segment, inverted T waves** and a **prolonged PR interval**. There may also be rhythm abnormalities such as **sinus bradycardia** , **ventricular extrasystoles, ventricular tachycardia** and **fibrillation**.



- Ludomirsky et al described three phases of cardiac toxicity following organophosphate poisoning:
- **Phase I: A brief period of increased sympathetic tone**
- **Phase II: A prolonged period of parasympathetic activity including AV node blockade**
- **Phase III: Q-T prolongation followed by torsade de pointes, ventricular tachycardia and ventricular fibrillation**

Respiratory manifestations



- Respiratory manifestations of acute organophosphorus poisoning include bronchorrhoea, rhinorrhoea, bronchospasm and laryngeal spasm.
- This is due to the action of the organophosphate on muscarinic receptors.
- The integrity of the airway may be compromised by excessive secretions.



- The nicotinic effects lead to weakness and subsequent paralysis of respiratory and oropharyngeal muscles.
- This increases the likelihood of both airway obstruction and aspiration of gastric contents.
- Finally, central neurological depression may lead to respiratory arrest

Neurological manifestations



- Three different types of paralysis are recognized based largely on the time of occurrence and their differing pathophysiology:
- Type I paralysis or acute paralysis
- Type II paralysis or Intermediate syndrome
- Type III paralysis or Organophosphate- induced delayed polyneuropathy

Type I paralysis or acute paralysis



- is seen during the **initial cholinergic phase**.
- This is when large numbers of both muscarinic and nicotinic receptors are occupied by acetylcholine, leading to persistent depolarization at the neuromuscular junction.
- **Clinical features** include muscle **fasciculation, cramps, twitching and weakness**.
- At this stage the patient may require ventilatory support due to the weakness of the respiratory muscles leading to respiratory depression and arrest.

Type II Paralysis/Intermediate syndrome



- The intermediate syndrome is a distinct clinical entity that occurs 24 to 96 hours after the ingestion of an OP compound.
- Approximately 10-40% of patients treated for acute poisoning develop this illness.
- The onset of the IMS is often rapid, with progression of muscle weakness from the:
 - **ocular** muscles
 - **neck** muscle (the patient cannot raise their head from the pillow)
 - **proximal** limbs
 - **respiratory muscles** (intercostals and diaphragm) over the course of 24 hours.

Clinical feature



- clinical manifestations of IMS typically **occur within 24 to 96 hours**, and affect **conscious** patients without fasciculation or other cholinergic signs.
- Marked weakness of neck flexion and varying degree of proximal limb muscle weakness, manifesting as weakness of shoulder abduction and hip flexion, are the constant clinical features.
- Respiratory insufficiency is common and frequently draws medical attention to the onset of the syndrome.
- Other possible manifestations are involvement of muscles innervated by motor cranial nerves and decreased deep tendon reflexes.
- **Sensory impairment is not** a clinical manifestation of IMS.

Type III paralysis or organophosphate- induced delayed polyneuropathy. (OPIDP)



- is a sensory-motor **distal** axonopathy that usually occurs after ingestion of large doses of an organophosphorus compound.
- The neuropathy presents as weakness and ataxia following a latent period of **2-4 weeks**.
- Initial stimulation causes excitatory fasciculation, which then progresses to an inhibitory paralysis. The cardinal symptoms are **distal weakness** of the hands and feet.



- This is often preceded by **calf pain**, and in some cases, **parasthesia** of the distal part of the limbs. Delayed CNS signs include tremor, anxiety and coma.

MANAGEMENT



DIAGNOSIS

- Diagnosis of OP poisoning based on the H/O exposure to OP compounds, characteristics manifestation of toxicity and improvement of sign and symptoms after administration of atropine.
- **Garlic-like smell** is an added clinical sign especially if the patient has ingested sulphur containing OP compound.
- This may be aided by insisting the patient attendant to search for a possible poison container in the vicinity of the patient.

Contd.



- Cholinesterase (ChE) estimations (plasma butyryl cholinesterase and red cell AChE) are the only useful biochemical tool for confirming exposure to OP.
- **Clinical severity** graded on the basis of the **pseudocholinesterase** level :-
 - ❖ Mild - 20-50% enzyme activity.
 - ❖ Moderate 10-20% enzyme activity.
 - ❖ Severe <10% enzyme activity.
- Though the enzyme activity does not correlate well with clinical severity.

Contd.



Plasma Butyrylcholinestrerase	Red cell acetylcholinestrerase
Easily assayed	Difficult to assay
Doesn't correlate well with neuronal activity .	Correlate well with neuronal activity 30% activity – normal muscle function < 10% activity – grossly deranged muscle function.
Response to antidotal therapy is less	Increased activity after pralidoxime therapy.
Levels altered in <u>malnutrition, chronic illness, chronic liver disease and infection.</u>	Levels altered in <u>hemoglobinopathies and thalassemia.</u>

Contd.



- Analytical identification of OP compound in gastric aspirate or in the body fluids gives the clue that patient has been exposed to OP compound.
- However in doubtful cases and especially if laboratory facilities are not available, **1 mg atropine can be given intravenously. If this does not produce marked anticholinergic manifestations, anticholinesterase poisoning should be strongly suspected.**

Treatment



- **Decontamination** and **Supportive** therapy
- Blockade of Muscarinic activity with **ATROPINE**.
- Reversal of cholinesterase inhibition with **OXIME**.
- Correction of **Metabolic abnormalities**
- Prevention of infection.
- Management of complication.

Decontamination and Supportive therapy



- Comatose or vomiting patients should be kept in left lateral, preferably head down position with neck extension to reduce the risk of aspiration.
- Patent airway should be secured with placement of airway or with endotracheal intubation especially if the patient is unconscious or having seizure.
- Frequent suctioning is essential as excessive oropharyngeal and respiratory secretions may occlude the airway.
- Need for oxygen therapy can be assessed by frequent assessment of arterial oxygen saturation.

Contd.



- All clothing, hair accessories are to be removed and placed in appropriate waste bags. The person is to be **washed with copious amount of water and soap.**
- Skin folds and underside of fingernails and long hairs require particular attention. Ocular decontamination is to be carried out by washing eyes with water/normal saline.
- The health care workers need protection through personnel protecting equipments. **Rubber** Gloves and gowns are recommended as these compounds are known to penetrate latex /vinyl gloves.

Contd



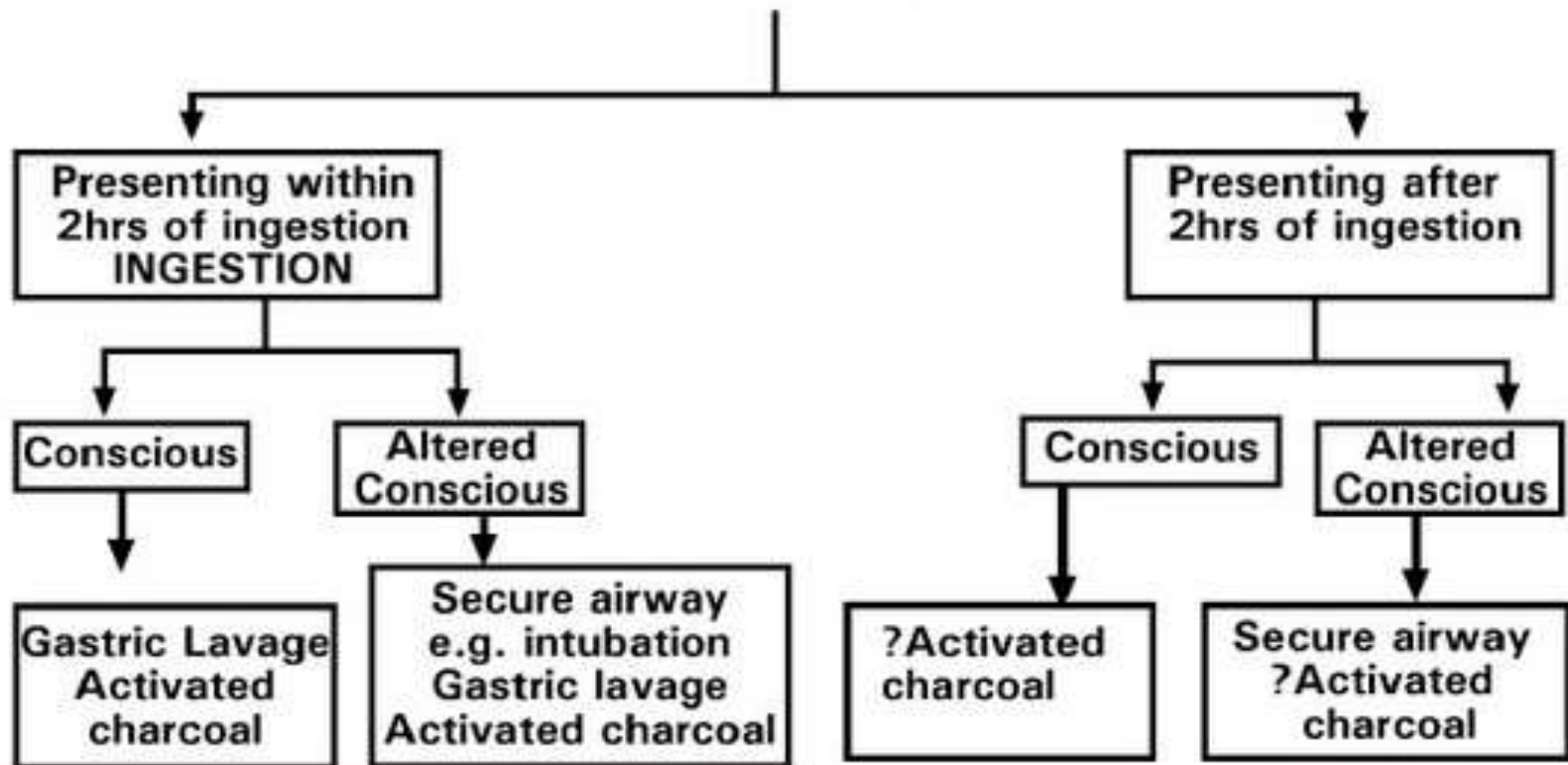
- **Gastric lavage**

- should be considered in patients presenting **within 1-2 hours** of ingestion of poison.
- Risks of gastric lavage include aspiration, hypoxia, and laryngeal spasm.
- reduced with proper management of airway.

- **Activated charcoal**

- reduce the poison load by adsorbing it.
- Its efficacy has not been conclusively proven in humans.
- single to multiple dose activated charcoal is routinely used in clinical practice.(25gm 2 hourly).
- AVOID cathartics and induced emesis.

OP Poisoning



Decontamination Procedure in OP Poisoning

Blockade of muscarinic activity with atropine



- Specific antidote for muscarinic effects, **no effect on nicotinic symptoms.**
- It reverses life threatening features that can result in death :
 - ❑ central respiratory depression
 - ❑ bronchospasm, excessive bronchosecretion
 - ❑ severe bradycardia, and hypotension.
- Current guidelines recommend the use of **incremental dose regimen** to attain target end points, followed by setting up an infusion to maintain these end-points.
- **Bolus dose regimen** (2-5 mg atropine every 10-15 min) found inferior to standard regimen.
- **Continous infusion regimen** (1 mg/min till full atropinisation) can be used in resource poor setting.

Contd.



- **Target end-points for Atropine therapy :**
 - Heart rate >80 / min.
 - Dilated pupils.
 - Dry axillae.
 - Systolic blood pressure >80 mm Hg.
 - Clear chest on auscultation with resolution of bronchorrhea (absence of wheeze and crepts).
- **Recommended dose** is an initial iv bolus of 1.8-3mg with subsequent doses doubled every 5 minutes if there is no response or repeat same dose until atropinization is achieved.
- **Maintenance dose:** 20% of initial atropinizing dose per hour for first 48 hours and gradually taper over 5 -10 days, continuously monitoring the adequacy of therapy.

Contd.



- Look for atropine TOXICITY
 - ❑ Agitation, confusion, hyperthermia, urinary retention and severe tachycardia.
 - ❑ can precipitate ischaemic events in patients with underlying coronary artery disease.
- Over atropinisation may necessitate discontinuation of the atropine infusion, followed by frequent observation.
- When they settle down the infusion is to be started at 70-80 % of the previous rate.
- Anticholinergic agent glycopyrrolate along with atropine can be used in order to limit the central stimulation produced by atropine.

Contd.



- Since **glycopyrrolate** does not enter CNS initial muscarinic signs like coma or drowsiness will not respond.
- It's use is recommended
 - ❑ when there is copious secretion as an adjunct to atropine
 - ❑ when features of atropine toxicity like delirium etc are confused with CNS effects of poison
 - ❑ when atropine is not available.
- **Dose** : 7.5 mg of glycopyrolate in 200ml of saline is started as infusion and is titrated to the desired effects of dry mucus membranes.

Reversal of cholinesterase inhibition by OXIMES.



- Oximes work by reactivating acetylcholinesterase that has been bound to the OP molecule.
- **Pralidoxime**
 - ❑ most frequently used oxime worldwide
 - ❑ Nucleophilic agent
 - ❑ other members include obidoxime and trimedoxime and experimental HI 6 and HLO 7.
- The therapeutic window for oximes is limited by the time taken for 'ageing' of the enzyme-OP complex, because 'aged' enzyme can no longer be reactivated by oximes.
- **Mechanism of action :**
 - ❑ Oximes get attached to the free anionic site of the enzyme ChE. The oxime end then reacts with the phosphorus atom of OP attached at the esteratic site of the enzyme. This **oxime phosphate** so formed **diffuses away leaving the enzyme intact** (Reactivated ChE).

Contd.



- **Dose :**
 - ❑ **WHO** recommends **pralidoxime** dose of 30 mg/kg bolus iv over 20-30 min followed by continuous infusion of 8mg/kg/hour Infusion continued until recovery : 12 hrs after atropine has been stopped and BChE noted to increase.
 - ❑ Largest oximes trial recommends 2gm loading dose followed by 500mg/hr maximum for 7 days .
- **Side effects** : Dizziness, headache, blurred vision, and diplopia, are common side effects of oxime therapy.
- Formation of stable phosphoryl oximes – high anticholinesterase activity.
- Rapid administration may lead to tachycardia, laryngospasm, muscle spasm, and transient neuromuscular blockade.

Treatment of complication



- **Cardiovascular complication :**

- ❑ Muscarinic receptor stimulation cause bradycardia and hypotension usually responds to atropine. Severe hypotension might benefit from vasopressors. The value of vasopressors versus higher doses of atropine is not yet clear.
- ❑ While nicotinic receptor stimulation cause sinus tachycardia and hypertension.
- ❑ ECG changes: Prolonged QTc interval, ST segment elevation, low amplitude T waves, extrasystole and prolonged PR interval.

- **Respiratory complication :**

- ❑ Regular and close observation in initial course will guide when to ventilate. Regular suctioning and high flow oxygen should be given to all patients with respiratory distress. Further, ABG should be done to guide the therapy.

Contd.



- **Indication of ventilator support :**

- I. Respiratory Gas Tensions

- i Direct Indices

- Arterial Oxygen Tension < 50 mm Hg on room air

- Arterial Co₂ Tension > 50 mm Hg in the absence of metabolic alkalosis

- ii Derived Indices

- P a o₂/ Fio₂ < 250 mm of Hg

- PA-aO₂ (Pulmonary arterial-alveolar O₂ gradient) > 350 mm of Hg

- II. Clinical - Respiratory Rate (RR) > 35 breaths/min

- III. Mechanical Indices

- Vital capacity < 15 ml/kg.

- Maximum inspiratory force $< - 25$ cm of H₂O.

Contd.



● CNS complication :

- ❑ Patients poisoned with organophosphorus frequently develop agitated delirium.
 - ❑ The cause is complex, with contributions from the pesticide itself, atropine toxicity, hypoxia, alcohol ingested with the poison, and medical complications.
 - ❑ **Diazepam** is first-line therapy for seizures; however, seizures are uncommon in well oxygenated patients with pesticide poisoning. Seizures seem to be more common with organophosphorus nerve agents (such as soman and tabun).
 - ❑ Animal studies suggest that diazepam reduces neural damage and prevents respiratory failure and death, but studies in humans are few.
 - ❑ **Gacyclidine** : anti-glutamatergic compound, inh. Seizure caused by nerve gas poison.
- Dose : 10 mg IV slowly which can be repeated up to 30-40 mg/24 hrs.

Supportive treatment



- **Antibiotic prophylaxis** :-
 - ❑ Broad spectrum antibiotics
 - ❑ risk of infection due to frequent and multiple interventions.
- **Hydrocarbon Aspiration** :-
 - ❑ ingestion of liquid concentrates of OP, hydrocarbon solvent aspiration causes chemical pneumonitis.
 - ❑ These cases are to be managed as a case of Acute Respiratory Distress Syndrome.
- **Furosemide** :- It is recommended if pulmonary oedema persists, even after full atropinisation.



- **Magnesium sulphate :-**

- ❑ **blocks** ligand-gated **calcium channels**, resulting in **reduced acetylcholine release from pre-synaptic terminals**, thus improving function at neuromuscular junctions, and reduced CNS overstimulation mediated via NMDA receptor activation.
- ❑ I/V MgSo₄ (4gm) on first day shown to decrease hospitalization period and improve outcome.

- **Clonidine :-**

- ❑ **alpha2-adrenergic receptor agonist.**
- ❑ **reduces acetylcholine synthesis and release** from presynaptic terminals.
- ❑ Animal studies show benefit of clonidine treatment, especially in combination with atropine, but effects in human beings are unknown.
- ❑ Dose : 0.15-.30 mg i/v bolus f/b 0.5 mg over 24hr.



- **Sodium bicarbonate :-**

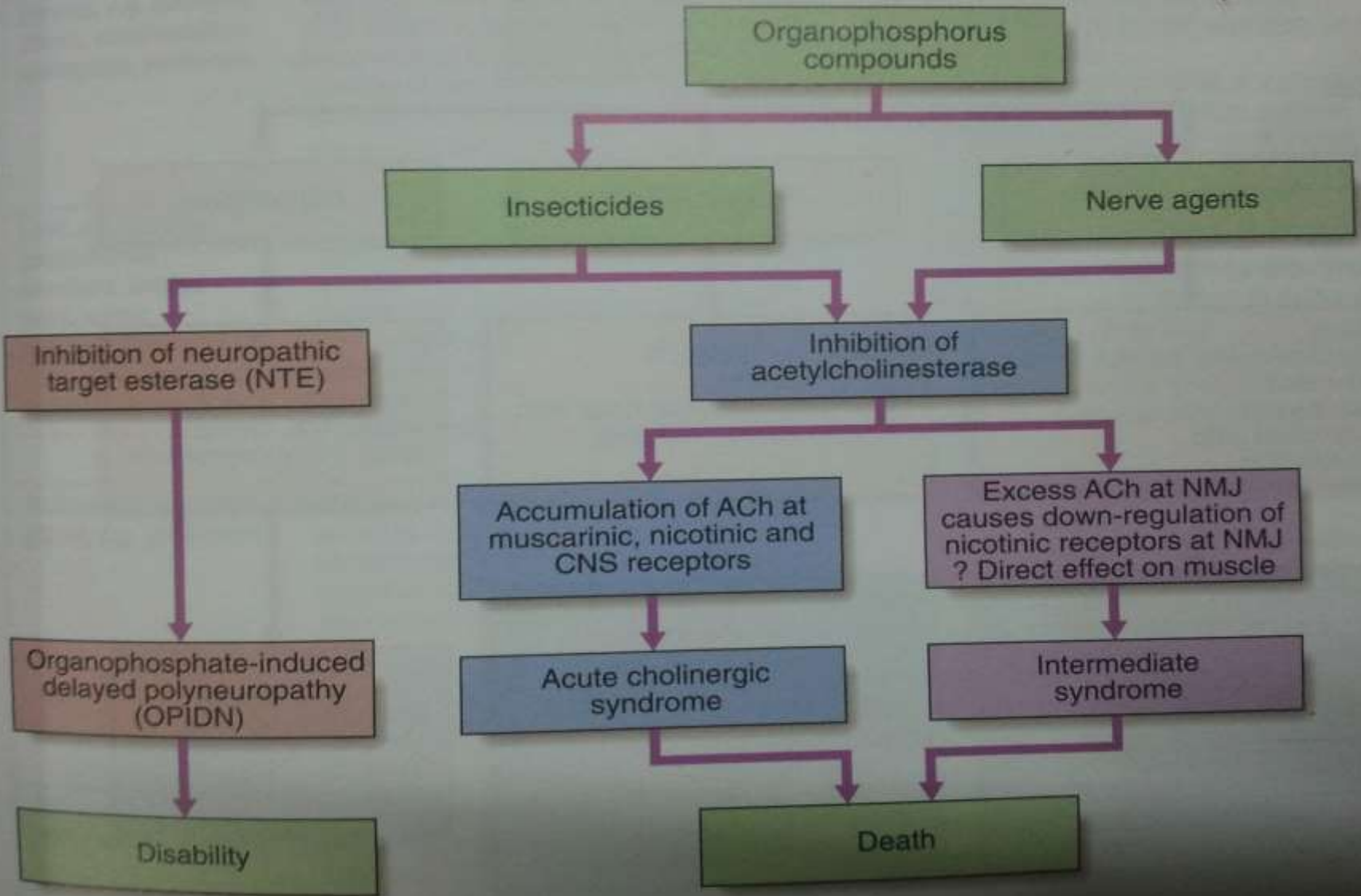
- ❑ Increases in blood pH (up to 7.45–7.55) have been reported to improve outcome in animals through an unknown mechanism.
- ❑ **Useful in nerve gas poisoning.**
- ❑ Dose : 5 meq/kg over 1 hour f/b 5-6 meq/kg/day.

- The roles of FFP, **haemodialysis** and **haemofiltration** are not yet clear.

- ❑ a recent non-randomised controlled study in China suggested a benefit of haemofiltration after poisoning with dichlorvos, which has poor solubility in fat, and therefore should have a relatively small volume of distribution.
- ❑ A systematic review of these therapies in organophosphorus poisoning is underway, but randomised controlled trials will be needed to establish good evidence-based treatment guidelines.



- A better approach than use of butylcholinesterase might be to give **recombinant bacterial phosphotriesterases or hydrolases**.
 - ❑ These proteins break down organophosphorus pesticides enzymatically and protect animals from pesticide poisoning.
 - ❑ Future clinical development of such enzymes could reduce blood concentrations of organophosphorus, allowing optimum activity of other treatments.



Mechanism of INTERMEDIATE SX



- IMS is well recognized as a **disorder of the neuromuscular junction**; however, its exact underlying mechanisms are not clearly defined.
- Senanayake and Karalliedde in their first report of IMS suggested that the syndrome might be caused by **pathologic change in the postsynaptic end-plate** region of striated muscles.
- Proposed mechanism of IMS are:
 - Downregulation or desensitization of postsynaptic Ach Receptors.
 - Prolonged Ach esterase inhibition.
 - Failure of postsynaptic Ach release.
 - Oxidative stress related myopathy.
 - Muscle necrosis.

Treatment of IMS



- Treatment of IMS is *mainly supportive* and there are no specific antidotes available for this devastating syndrome.
 - ❑ With supportive therapy, recovery from IMS occurs **5–18 days** after the onset of weakness.
 - ❑ Regression of toxic signs among patients who survived IMS followed a distinct pattern. **Muscle power first resumed in cranial nerve-innervated muscles, followed by respiratory muscles, proximal muscles, and neck flexors.**

Organophosphate induced delayed polyneuropathy (OPIDN)



- Occurs 1-3 weeks after acute exposure.
- Usually present with symptoms of cramping muscle pain followed by numbness and paraesthesia in distal upper and lower limb.
- Can cause foot drop, wrist drop, muscle wasting and deformity such as clawing of the hands.
- Physical examination :
 - ❑ Symmetrical flaccid weakness of the distal muscle
 - ❑ Variable sensory loss
 - ❑ Dominant hand affected more
 - ❑ Tendon reflex are lost or reduced ; absent ankle reflex being a constant feature

Pathophysiology of OPIDN



- Neuropathy inducing OP compounds cause inhibition of carboxylesterase i.e. **NTE** (neuropathy target esterase).
 - ❑ Inhibition should be irreversible and significant.
 - ❑ degeneration of distal regions of large, long myelinated axons as the primary lesion, which progresses to Wallerian-like degeneration of affected fiber regions.
- Inhibition of NTE is necessary antecedent to OPIDN but precise relationship has not been defined till now.
- Physiological function of NTE is not known.
- **Dichlorovos and nerve agent** are not associated with OPIDN.

Treatment



- Recovery from OPIDN is incomplete and may be limited to the hands and feet, although substantial functional recovery after 1-2 years may occur in younger patient.
- Currently no drug is approved for treatment of OPIDN.
- Following drugs are under trial :
 - ❑ Phenylmethylsulfonyl fluoride (PMSF)- serine protease inhibitor.
 - ❑ Corticosteroid and vitamin
 - ❑ Calcium channel blocker
 - ❑ Ganglioside mixture

Mortality



- Worldwide Mortality 3–25%.
- Mortality Rates Depend On The
 - Type Of Compound Used,
 - Amount Ingested,
 - General Health Of The Patient,
 - Delay In Discovery And Transport,
 - Insufficient Respiratory Management,
 - Delay In Intubation, And
 - Failure In Weaning Off Ventilatory Support.