STUDY ON NERVE CONDUCTION ABNORMALITIES IN ORGANO PHOSPHORUS POISONING

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CERTIFICATE

This to certify that the dissertation entitled **"STUDY ON NERVE CONDUCTION ABNORMALITIES IN ORGANO PHOSPHORUS POISONING"** is a bonafide original work of **Dr.S.SENTHIL KUMAR**, in partial fulfillment of the requirements for **M.D. Branch–I (Internal Medicine)** Examination of the **Tamilnadu Dr.M.G.R Medical University** to be held in March 2009.

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DECLARATION

I, **Dr.S. SENTHIL KUMAR,** solemnly declare that the dissertation titled, **"STUDY ON NERVE CONDUCTION ABNORMALITIES IN ORGANO PHOSPHORUS POISONING"** is a bonafide work done by me at Poison Control Training and Research Centre, Institute of Internal Medicine, Madras Medical College & Govt. General Hospital, during Jan. 2008 to June 2008 under the guidance and supervision of **Prof.C.RAJENDIRAN, M.D.,** Institute of Internal Medicine. The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in Internal Medicine.

Place: Chennai.

Date: **(Dr.S.SENTHIL KUMAR)**

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INTRODUCTION

Organophosphate induced delayed polyneuropathy (OPIDP) is an uncommon clinical condition. It occurs in association with the ingestion of large amounts of organophosphate after the stimulation of cholinergic receptors [(1)]. It is characterized by distal degeneration of some axons of both the peripheral and central nervous systems occurring one to four weeks after single or short-term exposures [(2)]. The prevalence of OPIDP in patients with organophosphate poisoning is nearly 22% [(3)].

The clinical sequence can be of three types: Type I syndrome (acute poisoning) is characterized by acute cholinergic effects appearing within a day of exposure to opc, often within hours. Cholinergic symptoms include tachycardia or bradycardia, diarrhea, vomiting, fasciculations, sweating, salivation and micturition, which are treatable with atropine [(4)]. Type II or Intermediate syndrome follows the intense cholinergic crises of organophosphate poisoning and occurs in up to 20 to 50% of cases depending on the severity of poisoning, its duration and the type of organophosphate compound. Their symptoms manifest 24 - 96 hrs after the poisoning on recovery from the cholinergic crises and include muscular weakness, affecting predominantly proximal limb muscles and neck flexors. Unlike the delayed polyneuropathy, this syndrome carries a death risk due to respiratory depression. The clinical course may last from 5 to 18 days [(5)]. Type III syndrome (OPIDP) is induced by many organophosphate esters (ops), may cause a distal dying back axonopathy characterized by cramping muscle pain in the legs, paresthesia and motor shortcoming beginning 10 days to three weeks

after the initial exposure. Associated signs include high stepping gait associated with bilateral foot drop, absent ankle jerks, weakness of intrinsic hand muscles and wrist drop. Sensory symptoms may be present but it is predominantly a motor neuropathy. Pyramidal tract involvement may also present. Diagnosis is based on history of organophosphate poisoning, clinical findings, electromyography and nerve conduction studies which show typical denervation pattern.

Organophosphate induced delayed neuropathy (OPIDN) is a sensory-motor distal axonopathy which usually occurs after the ingestion of large doses of certain organophosphate insecticides. Most of the patients developed a mixed polyneuropathy, mainly motor[6]. The neurotoxic effects of organophosphates have been well known since the dramatic outbreak of "Ginger Jake Paralysis", which crippled as many as 50 000 in the USA in the 1930's[7]. Since then several other epidemics have occurred in different regions such as in Sri Lanka[8]. In this epidemic area, adolescent Tamil girls attaining menarche or women right after childbirth were affected and developed polyneuropathy between fourteen and thirty days after gingili oil ingestion, following local customs and tradition. Recovery from OPIDN is considered to be generally poor. It is possible that several other factors such as the age of the patients, the difference in the chemical structure of the organophosphate and the duration of initial intoxication in some way contribute towards a favorable outcome[9].

REVIEW OF LITERATURE

HISTORY:

In the era of industrial revolution many organophosphorous compounds were synthesized. Organophosphates (OPs) are chemical substances originally produced by the reaction of alcohols and phosphoric acid. As early as 1854 Clermont prepared tetra ethyl pyrophosphate (TEPP) OPC made its mark in modern chemistry when Lange and Krueger recorded the synthesis of di-methyl di-ethyl phosphor fluoridates in 1932 [(10)]. They observed that inhalation of these compounds produced blurring of vision and choking sensation. But OPC as pesticides were produced by a group of German scientists led by Gerhard Schrader, Farben Febriken and Bayer 1937. The possibilities of potential chemical warfare with these agents were explored by Nazis in World War II. Indeed Sarin (isopropyl methyl phosphonofluoridate) was used by Iraq against Kurdish rebels in villages of north IRAQ [(11)]. The residues of Sarin were still found in analysis of the soil. In 1944 Schrader synthesized parathion which was widely used as a pesticide. In 1870 Fraser developed atropine as an antidote to physostigmine. Collomp in 1949 experimented atropine against muscarinic effects of nerve gas. In 1955 Davies introduced oximes and I.B Wilson confirmed its usefulness in acute opc poisoning. Namba for the first time used pralidoxime in his victims of opc poisoning in 1956. Lallement studied GK-11 an anti Glutamimetic drug as a neuro protective agent in OPC in 1997. In 1998 adenosine receptor antagonist role was studied in OPC necessitating further studies.

Historic and new uses of organophosphates:

The first organophosphate was synthesized in 1850. Physostigmine was used to treat glaucoma in the 1870s. By the 1930s, synthetic cholinesterase inhibitors were being used for skeletal muscle and autonomic disorders. Some organophosphates were tried in the treatment of Parkinsonism.

In 1986, testing began for tacrine, the first cholinesterase inhibitor to be tried for Alzheimer disease; it was released for clinical use in 1993. The blood-brain barrier has been the limiting factor in developing a cholinesterase inhibitor for use in dementia. A new drug, rivastigmine, is now available. Reported adverse effects are nausea and vomiting, with resultant weight loss because of the increase in cholinergic activity. It has been shown to be useful in mild to moderately severe Alzheimer disease.

Recently, pyridostigmine has been tried for the fatigue of post polio syndrome. Unfortunately, the study showed no benefit.

Table: 1: CLASSIFICATION AND THEIR STRUCTURE

Sl. No.	Common Name	Trade Name
1.	Acephate	Asataf, Orthene, Starthene
2.	Chlorpyrifos	Dursban, Durmet, Lorsban
3.	Dichlorvas	Noovan
4.	Dimethoate	Rogar, Tara 909, Fosfamid
5.	Fenitrothian	Surmunion, Nitrophos
6.	Fenthion	Baycid, Baytex
7.	Malathion	Cythion, Chemathion
8.	Methyl Parathion	Metacid, Folitav,
9.	Monocrotophos	Monocron, Nuvacron, Luphos
10.	Phorate	Thimet, Pempart
11.	Parathion	Folidol, Ekatox
12.	Phosphomidan	Dimecron, Famfos
13.	Quinalphos	Ekalux

GENERAL CHEMICAL STRUCTURE

Organophosphorous compounds are basically esters of phosphoric acid or of phosphorothioic acids [12].The R denotes either ethyl or methyl group. The organothiophosphates which contains double bonded sulphur group are converted into organophosphates in the liver. Phosphonate contains an alkyl(R-) in place of one alkoxy group (RO-). The X is called the leaving group and is the principal metabolite for species identification. [13].

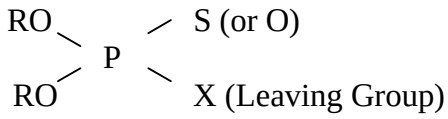


Table 2

Highly toxic:

Sl. no	Brand name	Chemical name
1	Dimecron	Phosphomidan
2	Folidol	Ethyl parathion
3	Celethion	Chlorthiophos
4	Systox	Demeton s methyl
5	Trithion	Carbophenothion
6	Moonbug, metacid	Methyl parathion
7	Bloom	Dichlorvas

Moderately toxic:

Sl. no	Brand name	Chemical name
1	Baytex	Fenthion
2	Entex	Formothion
3	Finit	Malathion
4	Tic 20	Fenitrothion
5	Spectacide	Diazinon
6	Canon, classic 20	Chlorpyriphos
7	Abate	Temephos

Others:

Sl. no	Brand name	Chemical name
1	Hydan, hinosan	Edephenophos
2	Kinadon, siccomedon	Phosphenidone
3	Josh, Shikari	Triazophos
4	Monocrown, monosul	Monocrotophos
5	Rogor, Digor	Dimethoate
6	Ekalux	Quinalphos
7	Actellic	Pirimiphos

KINETICS:

The kinetics of each group are highly dependent upon many factors such as route of administration such as ingestion, injection, inhalation, transdermal and transmucosal exposure, distance from target organs, local versus systemic metabolism and activation, route of elimination, endogenous hydrolysis and consumption of the compound by non specific esterases. Each group has its chemical structure, R- groups attached to the sulphur, carbon, or phosphorus entity, tightness of the bond to the central atom and the inherent affinity to cholinesterase. [(14)] After absorption the chemicals are equally distributed in all tissues but predominantly in liver and the renal. Lipophilic compounds reach maximum concentration in neural and other lipid rich tissues. Plasma half life after single dose administration depends upon the type of opc and route of exposure and it may range from few minutes to few hours. Metabolism occurs mainly by three ways namely oxidation, hydrolysis by esterases and transfer of

portion of molecule to glutathione. Urinary and faecal excretion occurs in 48hours where in 80- 90% of the compound is eliminated [15].Most of the agents show some symptoms and signs within six to ten hours [16] with the exception of fat soluble compounds where it may take several days to weeks to manifest because the substance must be leached out of the fat. Some opc have to be activated to active toxic state (hepatic activation of parathion to paraxon).Studies reveal that these residues may remain for days to week even after treatment. [17]

MECHANISM OF ACTION:

Acetylcholine (ACh) is the neurotransmitter released at all postganglionic parasympathetic nerve endings and at the synapses of both sympathetic and parasympathetic ganglia. It is also released at the skeletal muscle myoneural junction, and serves as a neurotransmitter in the central nervous system. ACh is hydrolyzed by acetyl cholinesterase into two fragments: acetic acid and choline.

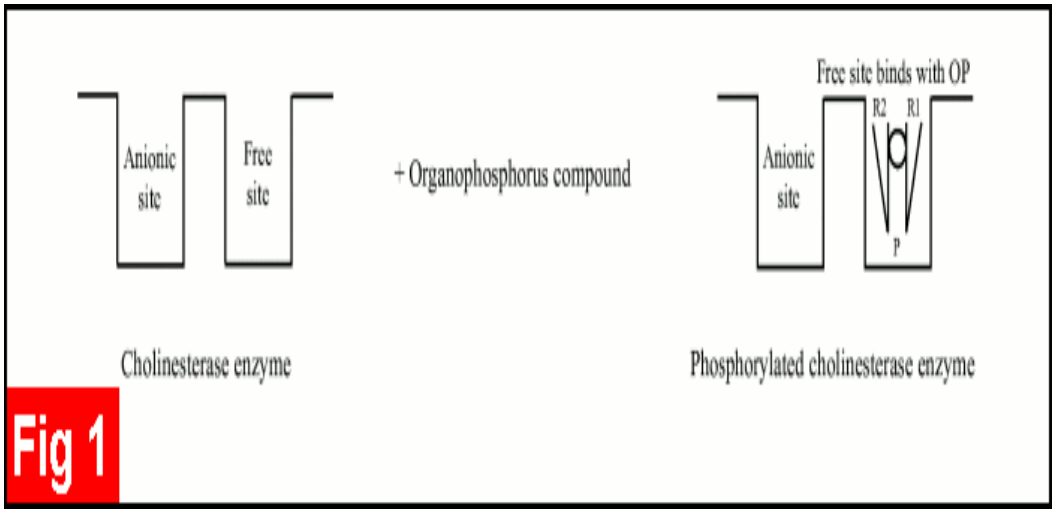
Acetyl cholinesterase is present in two forms: True acetyl cholinesterase which is found primarily in the tissues and erythrocytes, and pseudo cholinesterase which is found in the serum and liver.

Organophosphorous compounds are acid-transferring inhibitors of cholinesterase. They cause cholinesterase to become firmly (and sometimes irreversibly) phosphorylated. This means that the action of cholinesterase will be inhibited. Cleavage of the carbon-enzyme bond from ACh is complete in a few microseconds. However, the breaking of the phosphorus-enzyme bond

requires a period varying from 60 minutes to several weeks, depending on the organophosphorous compound involved.

Reactivation of the inhibited enzyme may occur spontaneously. The rate of reactivation will depend on the species, the tissue, and the chemical group attached to the enzyme. Reactivation may be enhanced by hydrolysis of the acid-radical-enzyme through the use of oximes (i.e. reactivating agents). Response to reactivating agent is declining with time. This process is being caused by "ageing" of the inhibited enzyme. Ageing is probably the result of the loss of one alkyl or alkoxy group, leaving a much more stable acetyl cholinesterase. The aged phosphorylated enzyme cannot be reactivated by oximes.

Accumulation of acetylcholine causes over stimulation of both muscarinic and nicotinic receptors, and subsequently disrupts the transmission of nerve impulses in both the peripheral and central nervous system. [17]



Most of these OPC do not possess a positive charge; hence they react with esteratic site but not with anionic site. Splitting of the acid group then occurs.

The bond between phosphorous and esteratic site (free site) is more stable than the bond between carbon atom of acetyl choline and the same site. Thus blocking of the active site and consequent inactivation of enzymes results in accumulation of acetylcholine at cholinergic sites. Pseudo cholinesterase is a less specialized enzyme as it lacks an anionic site in a position that specially adapts it to react with acetylcholine. It does however react with acetyl choline, albeit, more slowly and also with a wide range of other esters

BIOLOGICAL INTERACTIONS OF OPC [18]:

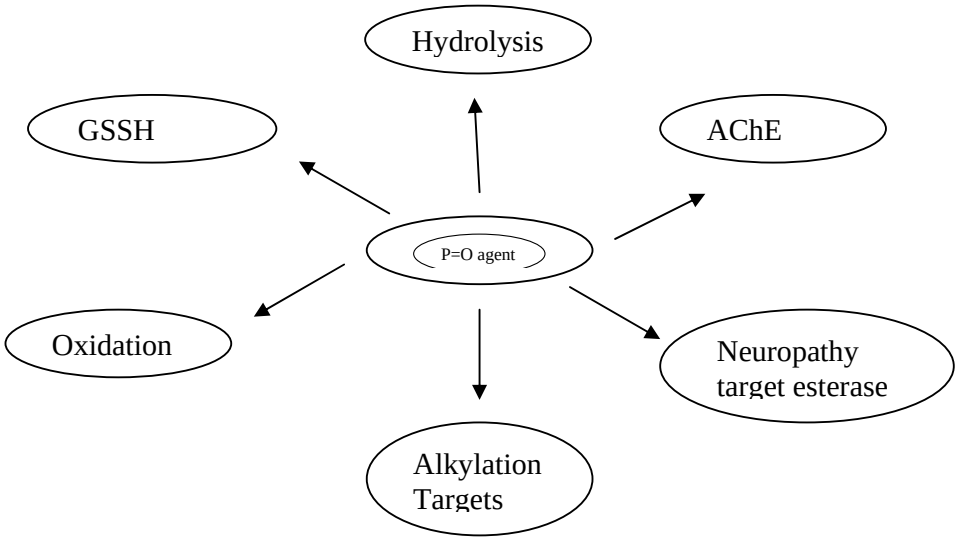


Fig.2

CLINICAL FEATURES

The clinical features depend upon the end points where sustained cholinergic stimulation takes place namely

a. Post ganglionic parasympathetic hollow end organ (muscarinic)

b. Sympathetic and parasympathetic ganglionic and somatic neuro muscular junction (nicotinic)

c. Central nervous system affection [19]

Following exposure to organophosphorous 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 organophosphorous compounds. Toxicity is produced by the rapid absorption of the compound through the gastrointestinal, respiratory tracts and skin.

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, diarrhea 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. 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, and 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.

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 blockade. Cardiac manifestations are often the cause of serious complications and fatality. [20].

Table 3. Symptoms and signs of organophosphorous poisoning

Muscarinic receptors	Nicotinic receptors	Central receptors
Cardiovascular • Bradycardia • Hypotension **Respiratory** • Rhinorrhoea • Bronchorrhoea • Bronchospasm • Cough **Gastrointestinal** • Nausea/vomiting • Increased salivation • Abdominal cramps • Diarrhea • Faecal incontinence **Genitourinary** • Urinary continence **Eyes** • Blurred vision • Increased Lacrimation • Miosis **Glands** • Excessive salivation	**Cardiovascular** • Tachycardia • Hypertension **Musculoskeletal** • Weakness • Fasciculation • Cramps • Paralysis	**General effects** • Anxiety • Restlessness • Ataxia • Convulsions • Insomnia • Dysarthria • Tremors • Coma • Absent reflexes • Respiratory depression • Circulatory collapse

The mechanism of cardiac toxicity is unclear and the following has been postulated:

- A direct toxic effect on the myocardium
- Over activity of cholinergic or nicotinic receptors causing hemodynamic alteration
- Hypoxia
- Acidosis
- Electrolyte abnormalities
- High dose atropine therapy (used as treatment for organophosphate poisoning).

RESPIRATORY MANIFESTATIONS:

Respiratory manifestations of acute organophosphorous 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.

GASTROINTESTINAL MANIFESTATIONS:

Symptoms resembling gastroenteritis such as vomiting, diarrhea and abdominal cramps are the first to occur after oral ingestion of an organophosphorous compound.

NEUROLOGICAL MANIFESTATIONS:

A large number of patients, following acute exposure to organophosphorous compounds, require prolonged ventilatory support in the intensive care unit due to neuromuscular weakness. The neurological manifestations have therefore been a primary focus of interest. There has been an emphasis on reducing the incidence of neuro-muscular respiratory failure. 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:

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 or Intermediate syndrome:

This was first described in 1974 by Wadia et al [20] as type II paralysis and subsequently termed "The Intermediate Syndrome" by Senanayake. This syndrome develops 24-96 hours after the poisoning. Following recovery from the acute cholinergic crisis, and before the expected onset of delayed neuropathy, some patients develop a state of muscle paralysis.

The cardinal feature of the syndrome is muscle weakness affecting the proximal limb muscles and neck flexors. There is a relative sparing of the distal muscle group. One of the earliest manifestations in these patients is the inability to lift their head from the pillow (due to a marked weakness in neck flexion). This is a useful test to establish whether or not a patient is likely to develop respiratory muscle weakness. Of the cranial nerves, those supplying the extra-ocular muscles are mostly involved, with a lesser effect on VII and X. This syndrome persists for about 4-18 days and most patients will survive unless infection or cardiac arrhythmias complicate the course.

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

Organophosphate-induced delayed polyneuropathy (OPIDP) is a rare toxicity resulting from exposure to certain organophosphorus (OP) esters. It is characterized by distal degeneration of some axons of both the peripheral and central nervous systems occurring 1-4 weeks after single or short-term exposures.

Cramping muscle pain in the lower limbs, distal numbness and paraesthesiae occur, followed by progressive weakness, depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. Signs include high-stepping gait associated with bilateral foot drop and, in severe cases, quadriplegia with foot and wrist drop as well as pyramidal signs. In time, there might be significant recovery of the peripheral nerve function but, depending on the degree of pyramidal involvement, spastic ataxia may be a permanent outcome of severe OPIDP. Human and experimental data indicate that recovery is usually complete in the young.

At onset, the electrophysiological changes include reduced amplitude of the compound muscle action potential, increased distal latencies and normal or slightly reduced nerve conduction velocities. The progression of the disease, usually over a few days, may lead to non-excitability of the nerve with electromyographical signs of denervation. Nerve biopsies have been performed in a few cases and showed axonal degeneration with secondary demyelination. **Neuropathy target esterase (NTE)** is thought to be the target of OPIDP initiation. The ratio of inhibitory powers for acetyl cholinesterase and NTE represents the crucial guideline for the etiological attribution of OP-induced peripheral neuropathy. In fact, pre-marketing toxicity testing in animals selects OP insecticides with cholinergic toxicity potential much higher than that to result in OPIDP. Therefore, OPIDP may develop only after very large exposures to insecticides, causing severe cholinergic toxicity. However, this was not the case with certain triaryl phosphates that were not used as insecticides but as hydraulic fluids, lubricants and plasticisers and do not result in cholinergic toxicity. Several thousand cases of OPIDP as a result of

exposure to tri-ortho-cresyl phosphate have been reported, whereas the number of cases of OPIDP as a result of OP insecticide poisoning is much lower. Finally, several observational studies on long-term, low-level exposures to OPCs that sometimes reported mild, inconsistent and unexplained changes of unclear significance in peripheral nerves are briefly discussed.

OTHER EFFECTS OF OPC MAY INCLUDE

- Neuropsychiatric effects: Impaired memory, confusion, irritability, lethargy, psychosis, and chronic organophosphate-induced Neuropsychiatric disorders have been reported. The mechanism is not proven.[21]

- Extra pyramidal effects: These are characterized by dystonia, cogwheel rigidity, and parkinsonian features (basal ganglia impairment after recovery from acute toxicity).

- Other neurological and/or psychological effects: Guillain-Barré–like syndrome and isolated bilateral recurrent laryngeal nerve palsy are possible.[22]

- Ophthalmic effects: Optic neuropathy, retinal degeneration, defective vertical smooth pursuit, myopia, and miosis (due to direct ocular exposure to organophosphates) are possible.

- Ears: Ototoxicity is also possible[23].

MODIFIED DREISBACH' CLINICAL CRITERIA – KARNIT [24]

GRADE I - Mild symptoms related to portal of entry.

Nausea, vomiting in case of ingestion

Cough, burning sensation in the chest in case of inhalation Mild systemic symptoms like headache, dizziness, weakness

GRADE II - Moderate systemic intoxication

Abdominal pain and diarrhea in case of ingestion.

Tightness in chest, difficulty in breathing in case of inhalation

Salivation, Lacrimation, sweating, papillary changes. Bradycardia, confusion, tremor, restlessness.

GRADE III - Severe systemic intoxication

Respiratory depression, generalized weakness

Cyanosis, peripheral circulatory failure,

Convulsion, coma.

DIAGNOSTIC CRITERIA [19]

- **INVESTIGATORY MODALITES: ESTIMATION OF CHOLINEESTERASE LEVELS:** Organophosphate (OP) toxicity is a clinical diagnosis. Confirmation of organophosphate poisoning is based on the measurement of cholinesterase activity; typically, these results are not readily available. Although RBC and plasma (pseudo) cholinesterase levels can both be used, RBC cholinesterase correlates better with CNS acetyl cholinesterase (AChE) and is, therefore, a more useful marker of organophosphate poisoning.

    - Measurement of RBC and plasma cholinesterase levels prior to treatment with pralidoxime (2-PAM). Monitoring serial levels can be used to determine a response to therapy.

    - RBC AChE represents the AChE found on RBC membranes, similar to that found in neuronal tissue. Therefore, measurement more accurately reflects nervous system OP AChE inhibition.

    - Plasma cholinesterase is a liver acute-phase protein that circulates in the blood plasma. It is found in CNS white matter, the pancreas, and the heart. It can be affected by many factors, including pregnancy, infection, and medical illness. Additionally, a patient's levels can vary up to 50% with repeated testing.

    - RBC cholinesterase is the more accurate of the 2 measurements, but plasma cholinesterase is easier to assay and is more readily available.

- Cholinesterase levels do not always correlate with severity of clinical illness.

- The level of cholinesterase activity is relative and is based on population estimates. Neonates and infants have baseline levels that are lower than adults. Because most patients do not know their baseline level, the diagnosis can be confirmed by observing a progressive increase in the cholinesterase value until the values plateau over time.

- Falsely depressed levels of erythrocyte cholinesterase can be found in pernicious anemia, hemoglobinopathies, use of antimalarial drugs, and oxalate blood tubes.

- Falsely depressed levels of plasma cholinesterase are observed in liver dysfunction, low-protein conditions, neoplasia, hypersensitivity reactions, use of certain drugs (succinylcholine, codeine, and morphine), pregnancy, and genetic deficiencies.

- Other laboratory findings include leukocytosis, hemoconcentration, metabolic acidosis, hyperglycemia, hypokalemia, and hypomagnesemia.

IMAGING STUDIES:

A chest radiograph may reveal pulmonary edema but typically adds little to the clinical management of a poisoned patient. 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 extra-systoles, 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 torsades de pointes, ventricular tachycardia and ventricular fibrillation [25]

THERAPEUTIC CONSIDERATIONS

Medical Care: Airway control and adequate oxygenation are paramount in organophosphate poisonings. Intubations may be necessary in cases of respiratory distress due to laryngospasm, bronchospasm, bronchorrhoea, or seizures. Immediate aggressive use of atropine may eliminate the need for intubation. [26] Succinylcholine should be avoided because it is degraded by acetyl cholinesterase (AChE) and may result in prolonged paralysis.

- Continuous cardiac monitoring and pulse oximetry should be established; an ECG should be performed. Torsades de Pointes should be treated in the standard manner. The use of intravenous magnesium sulfate has been reported as beneficial for organophosphate toxicity.[27] The mechanism of action may involve acetylcholine antagonism or ventricular membrane stabilization.
- Remove all clothing and gently cleanse patients suspected of organophosphate exposure with soap and water because

organophosphates are hydrolyzed readily in aqueous solutions with a high pH. Consider clothing hazardous waste and discard accordingly.

- Health care providers must avoid contaminating themselves while handling patients. Use personal protective equipment, such as neoprene or nitrile gloves and gowns, when decontaminating patients because hydrocarbons can penetrate non polar 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 ocular exposure using isotonic saline.

- If ingestion occurred within 30 to 60minutes placement of nasogastric tube and administration of activated charcoal in a dose, 1g/kg orally. Cathartics are contraindicated because of electrolyte imbalance. [28]

Atropine administration: 3-5mg rapid intravenous should be given to reach effective atropinisation. The adequate atropinisation is gauged by five parameters.

1. Pulse rate >85/min
2. Systolic blood pressure >80mmHg
3. Absence of lung crackles
4. Dry axilla
5. No constricted pupils [20]

Then after three to five minutes, if the parameters are not attained double the initial dosing. Atropine should be given in doubling dose pattern till adequate atropinisation.

Maintenance of atropinisation: 10- 20% of the bolus dose should be given as infusion in 100ml normal saline and the parameters are assessed every 15minutes. If there is inadequate atropinisation superimposed bolus in the dosage of 3-5mg should be given. Atropine should be tailored down hourly for six hours and then every two to three hours for the next 24hrs. Meticulous watch for atropine toxicity such as agitation, confusion, retention of bladder, hyperthermia, ileus and tachycardia should be done.

Glycopyrrolate can be used instead of atropine. It does not raise the heart rate [56].

OXIMES: PRALIDOXIME (2-PAM OR PROTO PAM) [29]

Cholinesterase reactivation

Oximes are nucleophilic agents that re-activate the phosphorylated acetyl cholinesterase by binding to the organophosphorous molecule. The use of oximes in acute organophosphorous poisoning has been a controversial subject for the last two decades as there have been very few randomized controlled trials that have addressed the role of pralidoxime (PAM).

Pralidoxime has three main actions

- A direct reaction converting the organophosphate to a harmless compound.

- A transient reaction protecting the enzyme from further inhibition.

- Reactivation of the inhibited alkyl phosphorylated enzyme to free the active unit (if given early enough)

The reactivating action of pralidoxime is most marked at the nicotinic skeletal neuromuscular junction. It does not reverse the muscarinic manifestations of organophosphorous poisoning. Pralidoxime should be started as early as possible to prevent permanent binding of the organophosphate to acetyl cholinesterase. Once this has occurred, receptor regeneration is required to allow recovery. The recommended dose of pralidoxime in organophosphorous poisoning is 500 mg/hr infusion for the first 48 hrs followed by 1 gm iv tds for another 3 days. Pralidoxime should be continued until adequate spontaneous ventilation is achieved by the patient. The effective plasma concentration is 4mg/litre and the patient should show signs of improvement 10- 40 minutes after its administration. Plasma and pseudo cholinesterase levels should ideally be monitored during treatment. Side effects of pralidoxime include drowsiness, visual disturbances, nausea, tachycardia and muscle weakness, so treatment should be reserved for potentially fatal cases. Fresh frozen plasma can also be used in the management of OPC [57]. There is no proven effective treatment for OPIDP till now. So prevention is only way.

PREVENTION AND EDUCATION

Improved regulation of the availability of pesticides, strict regulation of vendors, and modifications in packaging of pesticides may all help reduce the

use of organophosphates as poisons. Adequate provision of information to the public, regular training of health care providers, better availability of drugs / antidotes and the establishment of poison information centers will facilitate in reducing the morbidity and mortality related to organophosphorous poisoning. Insecticides should be kept out of reach of children, to prevent accidental poisoning. During agricultural spraying, proper precautions should be taken to prevent inhalation and accidental ingestion of the substance. The greatest incidence of organophosphorous poisoning was reported from Japan where there were 19,436 cases over a period of 17 years (1953-1969).WHO used data from 19 countries and reported approximately 5,00,000 cases of pesticide poisoning annually. Of these 99% belong to third world countries [(29)].In1981 the estimate was 75,000 cases annually and rose to 3million in 1983 and majority were under the age of 30 [(30)]. Pesticide poisoning contributes more than forty percent of cases in Poison Centre GGH Chennai. The mortality rate due to this poison is 42.29% (case register2001-2004). The victims are farmers of rural South India.

OBJECTIVES

1. To describe the epidemiology of organophosphorous poisoning in poison centre, Government General Hospital, Chennai.

2. To study the clinical profile of organophosphorous poisoning in poison centre, Government General Hospital, Chennai

3. To analyze the epidemiological and clinical factors in correlation to severity and outcome of organophosphorous poisoning in poison centre, Government General Hospital, Chennai.

4. To analyze the incidence of organophosphate induced delayed polyneuropathy in the patients admitted with OPC poisoning in poison centre, Government General Hospital, Chennai.

5 To study the correlation between the incidence of delayed polyneuropathy and the compound consumed, quantity, duration of hospital stay and ventilatory support.

MATERIALS AND METHOD

SETTING:

This study was conducted in the Poison control, training and research centre, GGH, Chennai in collaboration of Institute of Internal Medicine, Institute of Biochemistry and Institute of Neurology. It was a prospective study done during the period from September2007- September2008. 29 patients with history and clinical features suggestive of organophosphorous poisoning were selected irrespective of age and sex.

EXCLUSION CRITERIA

1. Patients with other pesticide poisoning were excluded (eg. Carbamate, organochlorous compounds) by clinical features and confirmed by thin layer chromatographic analysis of gastric aspirate.

2. Patients with other poisoning such as oleander, oduvanthazai, and drug over dosage (nicotine replacements, inocybe, clitocybe, pilocarpine, opioids, phenothiazines, bethanechol etc) known to mimic the clinical picture of organophosphorous poisoning were excluded.

3. Patients with known medical illness such as neuromuscular disorders like myasthenia gravis or muscular dystrophy, hypokalemic periodic paralysis and conditions known to alter biochemical parameters were excluded.

Patients with known history of exposure to organophosphorous compounds were taken into consideration. The reliability on exposure was

reinforced by definite history from the patients and their attendants. The container from which the poison where consumed were studied for the type and the quantity estimated. Each patient registered for the study went through detailed clinical evaluation as per the proforma. The cases were divided into three groups as mild, moderate and severe by modified DREISBACH criteria. All patients underwent baseline laboratory investigations. The gastric aspirate was analyzed by thin layer chromatography method for the detection of poison.

All patients underwent complete Hemogram, renal function test, liver function test, ECG, chest roentgenogram, ultra sonogram of the abdomen and nerve conduction studies.

Serum AChE was measured on day 1, 2 and 3.

The other biochemical markers such as liver enzymes and amylase were taken on day1.

BI0CHEMICAL MARKERS AND THE METHODS EMPLOYED-(KITS)

1. CHOLINESTERASE	-	KINETIC COLORIMETRIC METHOD [31]
2. SGOT (AST)	-	UV KINETIC METHOD [32]
3. SGPT	-	(MODIFIED IFCC METHOD) [33]
4. ALKALINE PHOSPHATASE	-	PNPP METHOD [34]

5. ALBUMIN - BCG METHOD[35]

6. CK - UV KINETIC METHOD [36]

7. AMYLASE - CNP – G3 METHOD [37]

8. LDH - UV KINETIC METHOD [33]

Ventilatory support was considered in patients with following parameters

a. RR >35/min

b. Apnea or obvious hypoventilation

c. Persistent cyanosis, excessive secretions, depressed level of consciousness, inability to protect the air way [34]

d. PaO2 < 60 mmHg, FiO2 >0.6

PaCO2 > 50 mmHg, pH <7.2

Mechanical ventilation was performed with assist control mode and SIMV either as volume or pressure control. Positive end expiratory pressure was titrated to keep SaO_2 above 94% with 40% FIO_2. Weaning was performed using either T-tube trials or pressure support weaning. All patients were monitored meticulously and vital signs assessed till the outcome.

Detailed evaluation of each patient was made. Each variable in the pro-forma was correlated with severity and mortality.

RESULTS

Epidemiological Pattern of OPC in Poison Centre, Govt. General Hospital

Table: 4 - Age Distribution

Sl.No.	Age Group in years	Frequency(n)	Percentage
1.	< 20	3	10.4
2.	21-30	12	41.4
3.	31-40	5	17.2
4.	> 40	9	31.0
	Total	29	100.00

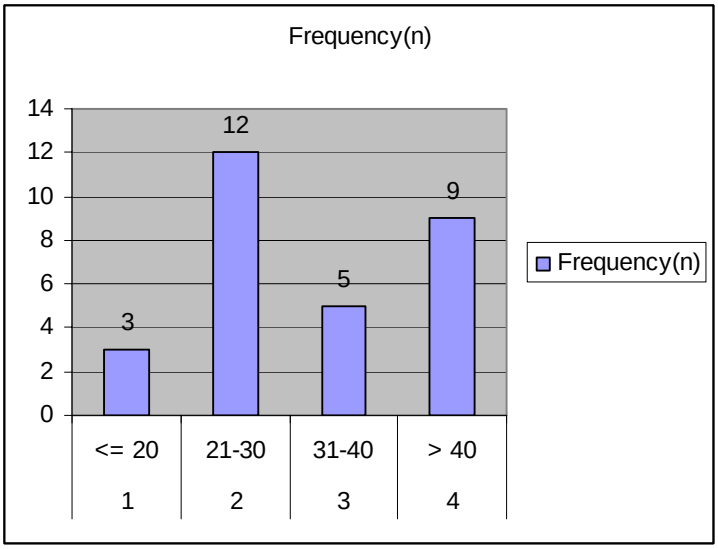


Fig: 3 - Age Distribution

Majority of the patients were in the 21 to 30 age group. The number of people between the age group 20 to 40 accounts for 59%.

Table: 5 – Age Distribution and Outcome

Sl.No.	Age Group in years	Death	Percentage
1.	<= 20	1	3.4
2.	21-30	1	3.4
3.	31-40	0	0.0
4.	> 40	3	10.3
	Total	5	100.00

Three people in the age group of above forty died. The percentage is 10.3%

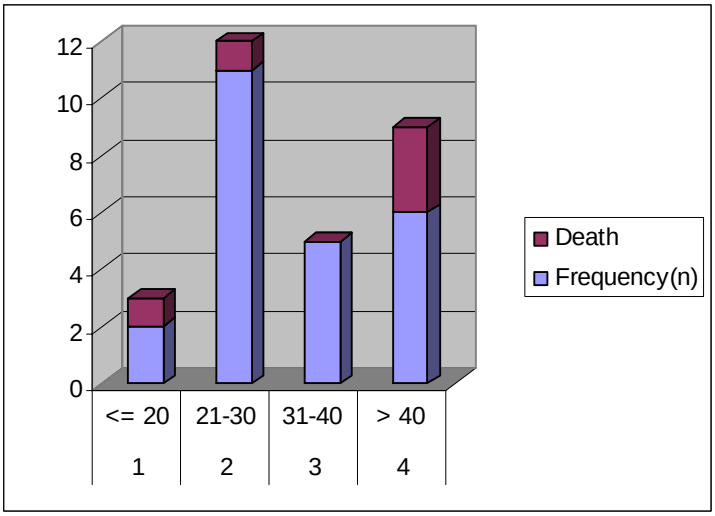


Fig: 4 – Age Distribution and Outcome

Table 6 Sex Distribution

Sl.No.	Sex	Frequency(n)	Percentage
1.	Male	24	82.8
2.	Female	5	17.2

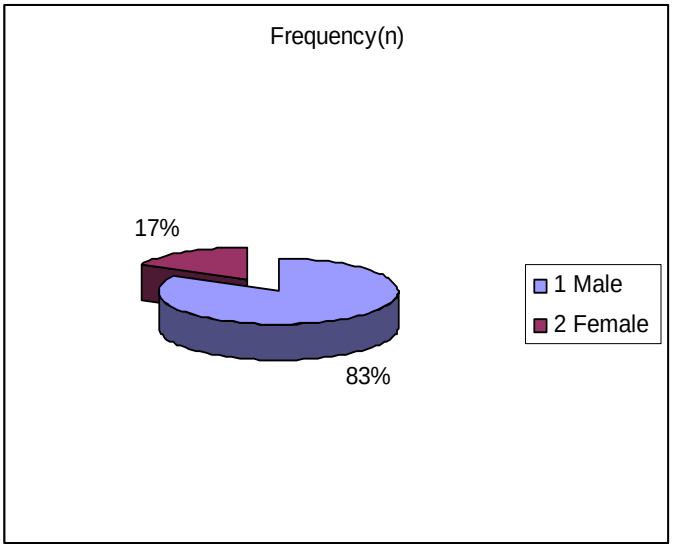
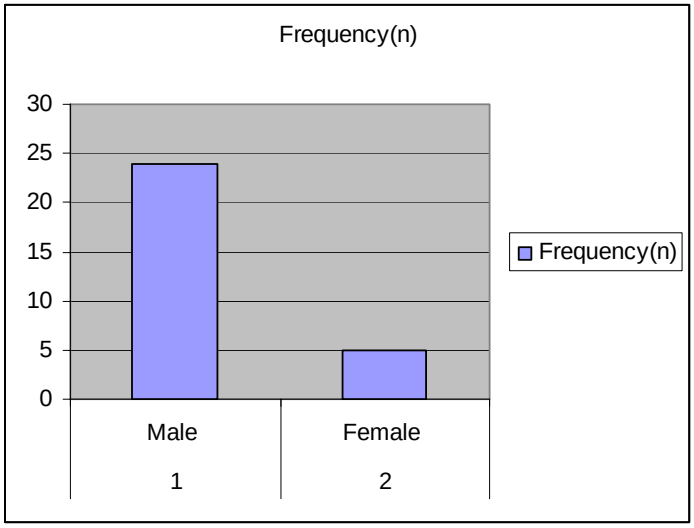


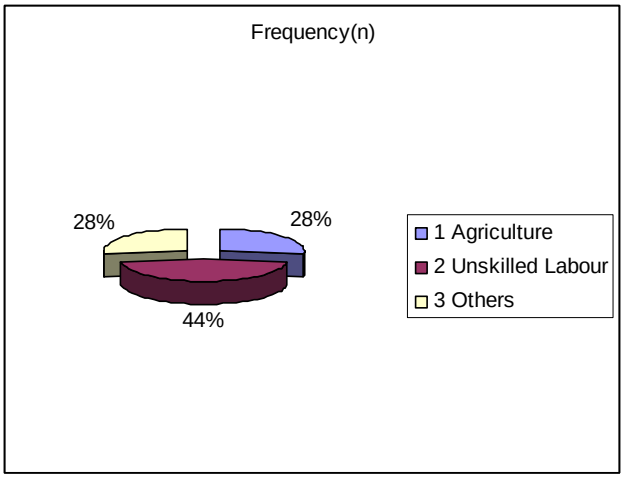
Fig: 5- Sex Distribution



Incidence of OPC was more in males when compared to females in our series. 24 out of 29 patients are males.

Table 7 - Occupation

Sl.No.	Occupation	Frequency(n)	Percentage	Expired
1.	Agriculture	8	27.6	1
2.	Unskilled Labour	13	44.8	2
3.	Others	8	27.6	2



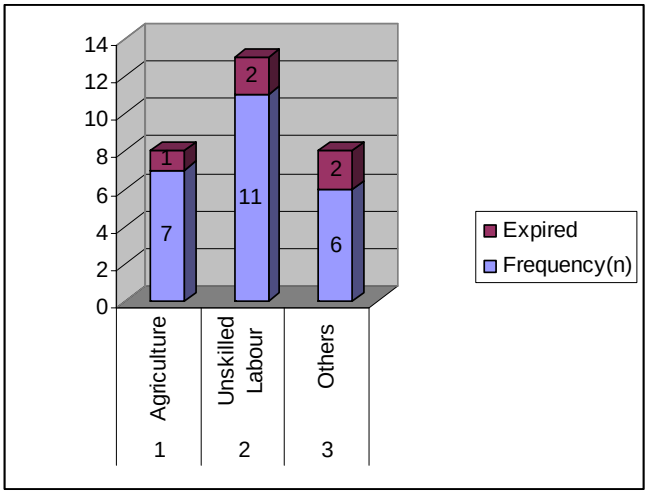


Fig: 6- occupation

More than 40 percent of the cases of OP poisoning were unskilled labors. Farmers made up 25%.

Locality:

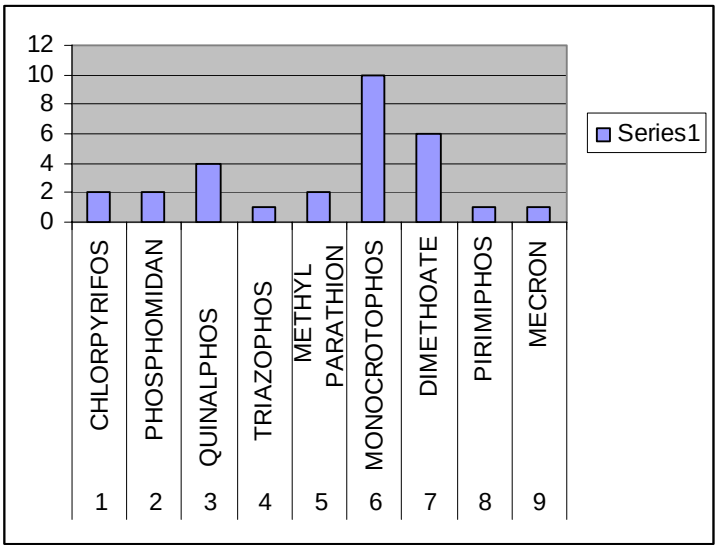
Distance from the Poison Centre, Govt.General Hospital in Kilo Meters.

Table 8 – Locality

Sl.No.	Locality (kms)	Frequency(n)	Percentage
1.	<= 100	12	41.4
2.	> 100	17	58.6

Table 9 - Type of Poison consumed

Sl.No.	Type of Poison consumed	Frequency(n)	Percentage
1.	CHLORPYRIFOS	2	6.8
2.	PHOSPHOMIDAN	2	6.8
3.	QUINALPHOS	4	13.8
4.	TRIAZOPHOS	1	3.4
5.	METHYL PARATHION	2	6.8
6.	MONOCROTOPHOS	10	34.4
7.	DIMETHOATE	6	20.6
8.	PIRIMIPHOS	1	3.4
9.	MECRON	1	3.4
	Total	29	100.00



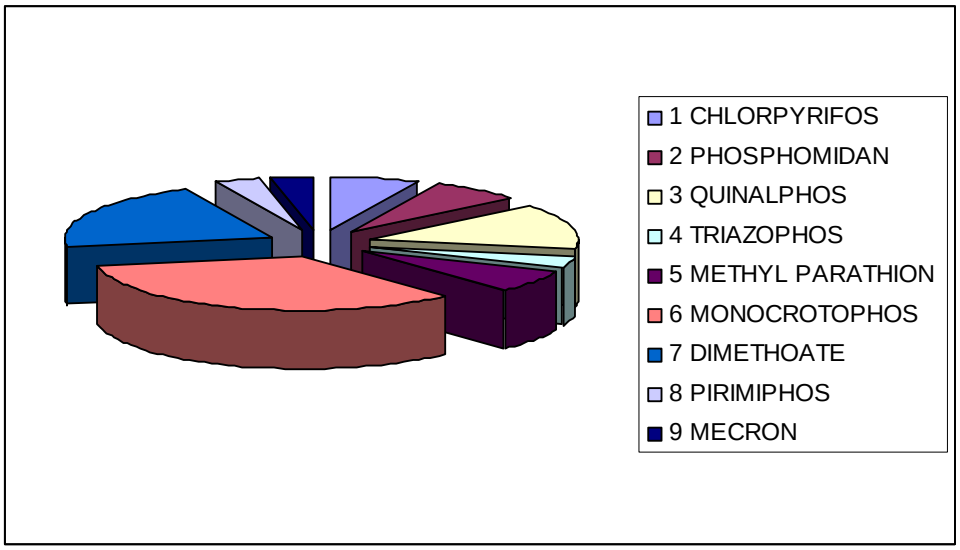


Fig: 7- Type of poison consumed

Most of the patients in this series consumed Monocrotophos (n=10) and Dimethoate (n=6). Four patients consumed Quinalphos.

Table.10- Route of Exposure

Sl.No.	Route of Exposure	Frequency(n)	Percentage
1.	Ingestional	27	93.2
2.	Inhalational	1	3.4
3.	Topical	1	3.4

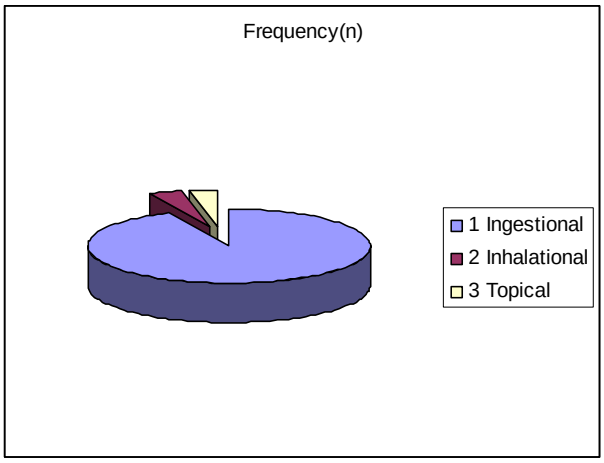
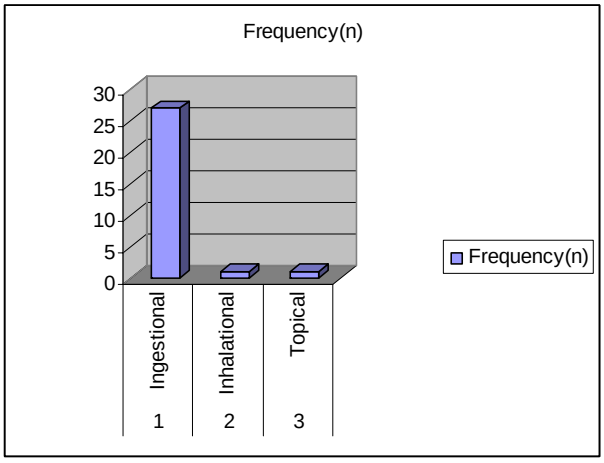


Fig: 8- Route of exposure



Ingestional exposure was more common among in the series (93.2%) and all of the patients in this entity fell under the severe grade of Dreisbach's criteria

Table 11: Intention of Poison:

SL. No:	Intention	frequency	percentage
1	Suicidal	28	96.6
2	Accidental	1	3.4

In this series 28 patients consumed OPC with suicidal intention. [96.6%]

Table.12 Duration of stay in hospitals

Sl.No.	Duration of Stay in Hospitals (in days)	Frequency(n)	Percentage
1.	<= 5	7	24.1
2.	6-10	10	34.5
3.	> 10	12	41.4
		29	100.00

The mean duration of stay in the hospital is 7.25 days (SD 4.64)

Table 13 :Quantum of exposure

Sl.No.	Quantity consumed (ml.)	Frequency (n)	Percentage
1.	NA	3	10.3
2.	<=50	4	13.9
3.	51-100	13	44.9
4.	>100	9	30.9
	Total	29	100.00

The non availability of data in 3 patients was due to two reasons.

1. Two cases had inhalational and topical forms of exposure so the quantity cannot be ascertained

2. Patient did not know the quantity of consumption

The average quantity of consumption in this series amounts to 101.58ml.

PERIOD INTERVAL FOR INITIATION OF TREATMENT

a) Initiation of First Aid (Gastric Lavage/activated charcoal)

Table 14: Initiation of First Aid

Sl.No.	Initiation of First aid (Hours.)	Frequency (n)	Percentage
1.	<=1	21	72.4
2.	1-2	6	20.7
3.	>2	2	6.9
	Total	29	100.00

Out of 29 patients 27 received first aid in a medical facility within two hours.

LABORATORY PARAMETERS:

1. Average hemoglobin observed in this series – 12.7 g/dl (SD =1.66)

2. Total WBC count had a range between 4800 and 23600 cells per cubic mm. and it had a mean value 8686 (S.D-3433)

3. Routine Bio-chemistry

Table 15: Bio Chemistry Values

Sl.No.	Values	Mean	S.D. (+/-)
1.	Blood Sugar mg/dl.	104.5	33.96
2.	Urea mg/dl.	30.7	9.4
3.	Creatinine	0.83	0.18
4.	Sodium	134	6.3
5.	Potassium	3.83	0.55

4. Liver Function Test: These parameters did not have any correlation with severity or outcome. The values of 29 patients are given below:

Table 16: LFT

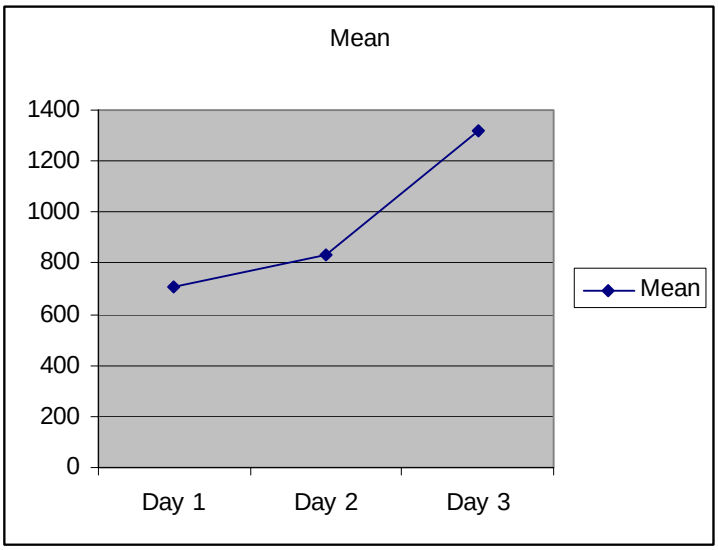
Sl.No.	Values	Mean	S.D. (+/-)
1.	SGOT IU/L	37.05	16.8
2.	SGPT IU/L	32.0	10.0
3.	Total Protein g/dl	6.51	0.50
4.	Albumin g/dl	3.70	0.78
5.	SAP IU/L	96.1	28.2
6.	Bilirubin	0.76	0.11
7.	Amylase	101	30.7

Pseudo cholinesterase Levels in OPC poisoned Patients

Table 17: Pseudo cholinesterase Levels in OPC poisoned Patients

Serum ChE Level IU/L	N	Mean	SD	Minimum Value	Maximum Value	Range
Day 1	29	706.3	833.8	134	4317	4183
Day 2	29	833.8	892.9	141	4585	4444
Day 3	27	1321.1	1012.1	148	3216	3068

In this series, sequential post exposure estimations of the ChEs up to 3 days revealed significant rise in the values correlated with substantial clinical improvement.



Pseudo cholinesterase Levels in OPC poisoned Patients

SERUM AMYLASE

In all 29cases, serum amylase and ultra sonogram of the abdomen were done. Sonography of the abdomen was normal in all cases. The mean serum amylase level in the series 101 U/L. (SD – 30.7)

VENTILATORY SUPPORT

Out of 29 patients 21 needed ventilatory support (72.4%). All patients were initiated on assist control mode.

The average duration of mechanical ventilation in the series was 9.2days (S.D=6.56). 5 out of 21 cases on mechanical ventilation expired .The morality rate among patients on mechanical ventilation was 23.8%. The mortality rate differed with patients with ventilatory support and with that of no support (0.0%).

Table 18 - Ventilatory Support & Outcome

	Ventilatory Support	No Support
No. of Patients	21	8
Recovered	16	8
Expired	5	0

Ten cases needed Tracheostomy during mechanical ventilation (34.5%)

Nerve conduction studies:

24 patients underwent nerve conduction studies in the third or fourth week of hospital stay according to the clinical severity. In the nerve conduction study, compound muscle action potential, sensory nerve action potential and nerve conduction velocities were measured in all four limbs. The normal values of these parameters were taken as controls. Thirteen patients had evidence of

OPIDP. Three patients had evidence of significant axonopathy, 6 patients had evidence of demyelination and 8 patients had evidence of sensory neuropathy. One patient had evidence of axonopathy, demyelination and sensory neuropathy and two patients had evidence of axonopathy and sensory neuropathy. One patient had evidence of demyelination and sensory neuropathy. Five patients had evidence of demyelination alone and four patients had evidence of sensory neuropathy alone. All Patients with axonopathy also had evidence of either demyelination or sensory neuropathy or both.

Table 19: Nerve conduction abnormalities:

Sl. No.	Type of Poison Consumed	Frequency (n)	Death	Axonopathy	Demyelination	Sensory neuropathy
1	Chlorpyrifos	2	0	0	0	1
2	Phosphomidan	2	1	0	0	0
3	Quinalphos	4	0	0	1	0
4	Triazophos	1	0	0	0	0
5	Methyl parathion	2	0	0	1	0
6	Monocrotophos	10	3	1	4	3
7	Dimethoate	6	1	2	1	1
8	Pirimiphos	1	0	0	0	1
9	Mecron	1	0	0	0	0
	Total	29	5	3	7	6

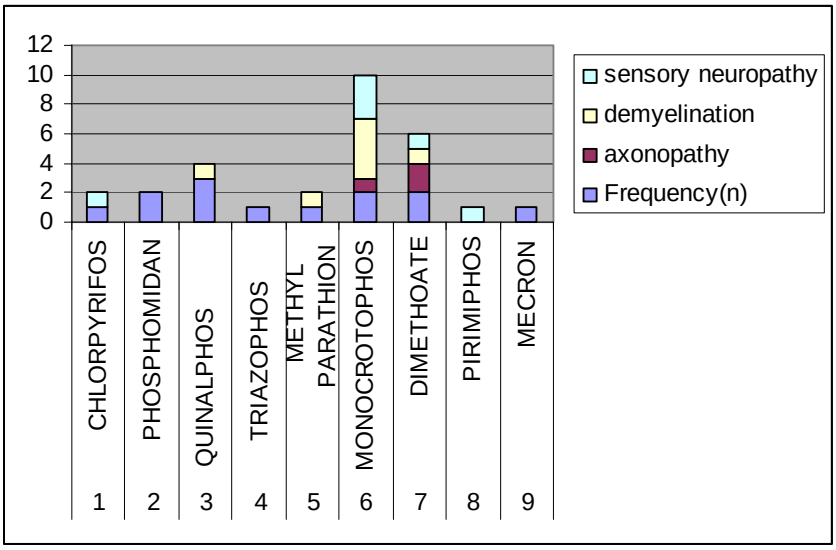


Fig: 9- Nerve conduction abnormalities

Outcome

In this series 5 patients expired. The mortality rate was 17.2%. In all cases primary cause of death was respiratory failure with secondary cardiac arrest. It has resulted from central respiratory depression, respiratory muscle weakness, increased bronchial secretions, bronchospasm and acute pulmonary oedema. All cases needed ventilatory support.

Out of these five deaths, three was due to ingestion of Monocrotophos. One was due to Dimethoate and the other was due to Phosphomidan.

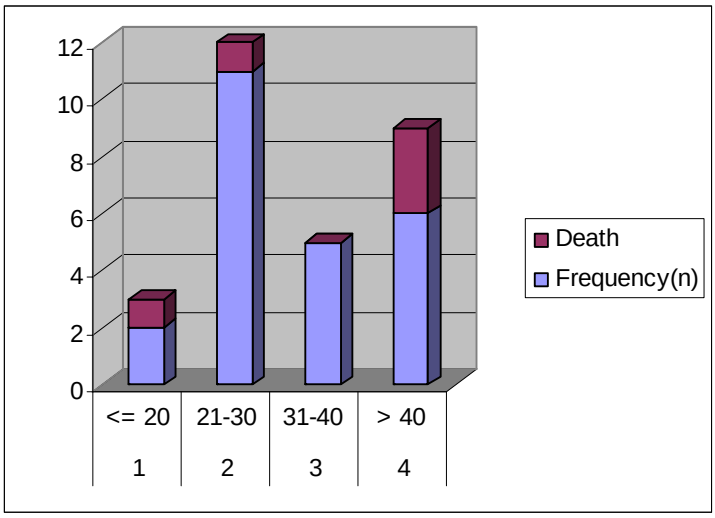
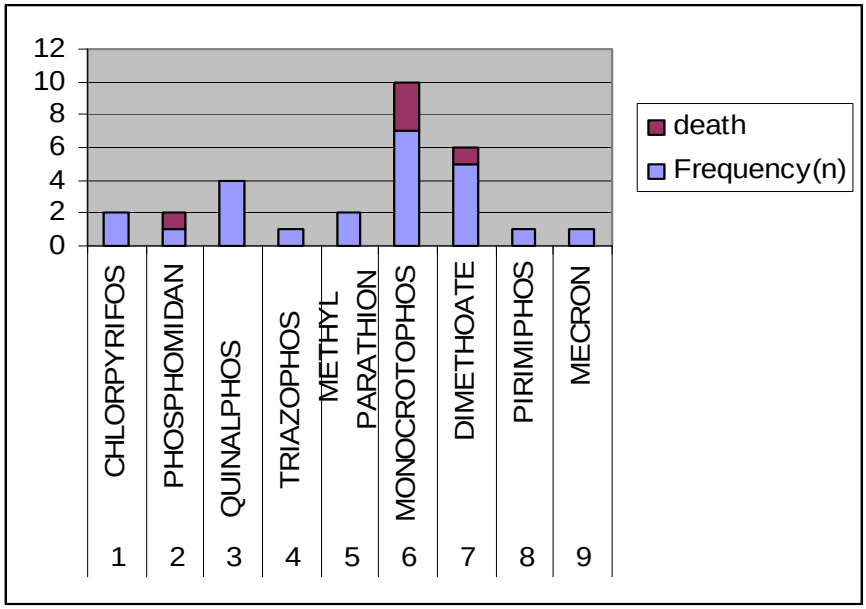


Fig: 10- Outcome

Table 20: Agents causing death

Sl.No.	Type of Poison consumed	Frequency (n)	Percentage	Death
1	CHLORPYRIFOS	2	6.8	0
2	PHOSPHOMIDAN	2	6.8	1
3	QUINALPHOS	4	13.8	0
4	TRIAZOPHOS	1	3.4	0
5	METHYL PARATHION	2	6.8	0
6	MONOCROTOPHOS	10	34.4	3
7	DIMETHOATE	6	20.6	1
8	PIRIMIPHOS	1	3.4	0
9	MECRON	1	3.4	0
	Total	29	100	5



In this series ten patients were admitted after consuming Monocrotophos. Out of these ten patients, three were expired. In the remaining seven one developed axonopathy, four patients developed demyelination and two patients developed sensory neuropathy.

In this series six patients were admitted with Dimethoate ingestion. One patient was expired. In the remaining five, two patients developed axonopathy.

DISCUSSION

Comprehensive analysis of 29 cases of acute organophosphorous poisoning.

EPIDEMIOLOGY OF ORGANOPHOSPHOROUS POISONING:

Age pattern:

In this series 15 cases were below the age of 30.WHO has reported about 3million cases of opc exposure and 40,000 deaths annually and majority were under the age group of thirty. [30] Murat Sungur and Muhammed Güven et al of turkey observed the mean age group of opc exposure was 30±15 years.[18] Karalliedde L, Senanayake N.et al of SRILANKA documented 91% of their cases were under the age of 30.[40]. In Kashmir valley Malik et al. revealed that 33.5% of the cases of opc were under the age of 25. [41] In Mangalore, Karnataka, India the most common age group to be affected was 20-30 tears (36.6%) [30]. The series reported in this thesis had the similar pattern of age group affection. The reason could be that this age group, by all probability, is vulnerable to various emotional conflicts that occur during this phase of life. This young age group affected by exposure form the viable entity of any population both in terms of procurement and productivity. This case study and the case reports mentioned above throw light on the target age group for educative and preventive programmes to reduce the incidence of opc poisoning.

SEX DISTRIBUTION

In poison centre GGH Chennai males were exposed more when compared to female population.(82.8% versus 17.2%). On the contrary to the series in Murat Sungur study of 47 cases of opc in Turkey [18] [(female n=25, male=22)] and. Malik et al. Observation of 122 cases in Kashmir valley [(female n=114, male=50)] female intoxication was more [41]. In Srilanka and Mangalore had similar pattern to the case series of the poison centre.(male 86%-female 14%).S.Shivakumar and K.Raghavan et al of Tamilnadu reported 165 cases of organophosphorous poisoning and sex distribution was similar to the case series (male n=122, female n=45)[38].This variation was due to handling of poison by the respective sex in their respective locality. In Kashmir the female populations are predominantly employed in apple orchards and they are involved in pesticide control. In southern part of India males are actively involved in spraying fertilizers and pesticides.

OCCUPATION AND SOCIOECONOMIC STATUS

Wesselling C, McConnell R, Partanen T, Hogstedt C et al reported that large worker populations in the Third World were exposed to increasing amounts of pesticides, including pesticides severely restricted and banned in industrialized countries. Studies on knowledge, attitudes, and practices indicate that unsafe use of pesticides was the rule in Third World countries [43].In our case series 21 out of 29 cases were agriculturists and unskilled labourers. In Kashmir valley, two third of the population who had exposure were engaged in apple orchard. In Karnataka, agriculturists formed the majority. Students

formed the predominant group in Nepal [44] whereas in Almeria exposure was more in green house workers [45].

INTENTION OF POISON:

Estimates from the WHO indicate that each year, 1 million accidental poisonings and 2 million suicide attempts involving pesticides were happen worldwide [46]. In the series majority of cases were suicidal in nature which was consistent with other workers. 28 cases (96.6%) were suicidal and 1 case (3.4%) had accidental exposure.

Murat Sungur and Muhammed Güven et al observed 68%of opc poisoning reported was of suicidal exposure and Karalliedde L, Senanayake N et al of SRILANKA had similar pattern. Malik et al. reported 74.4% of cases were of suicidal in nature and rest (25.6%) had accidental exposure. Palimar Vikram MD**,** Arun M MD, DNB et al in their case study of 153 cases in Mangalore reported 98.7%of suicidal exposure. Most of the agriculturists consume for the fact of failure of crops, increasing debts coupled with the easy availability of poison.

2700 people are referred to hospital for self poisoning each week in the United Kingdom alone [47]. It is likely to be even more difficult for the developing world, with its limited resources, to address this problem effectively. However, we think that the time has come to acknowledge the seriousness of the situation as a first step towards preventing this massive unnecessary loss of life.

ROUTE OF EXPOSURE:

Ingestion of the OPC poisoning (n=27) formed the majority in this series apart of inhalational (n=1) and topical (n=1) form of exposure. Arup Kumar Kundu, JD Mukhopadhyay**,** AK Saha, S Das et al [(48)]studied 108 patients in sub urban West bengal poison.90 consumed the poison and the death rate was12% and it had positive correlation with outcome. In Kashmir Valley out of 164 cases-ingestional route (n=140), inhalational (n=7) and topical exposure (n=17). In the Turkey study the gastrointestinal route was the main route in 44 (93.6%) patients.

TYPE OF POISON

In this study Monocrotophos (n=10 34.4%), Dimethoate (n=6 20.6) and Quinalphos (n-4 13.8%) were the most common type of poison consumed when compared to other workers.

Monocrotophos was consumed by ten patients. In these three were expired. In the remaining seven, one developed axonopathy, four developed demyelination and two developed sensory neuropathy.

Six patients were admitted with Dimethoate ingestion. One patient was expired. In the remaining five, two patients developed axonopathy.

Murat Sungurb et al in turkey observed the three common type of opc were:

Agent	Number of patients
Dichlorvas	24 (51.1%)
Ethyl-Parathion	5 (10.6%)
Fenthion	4 (8.5%

In sub urban West Bengal Arup kumar kundu et al showed that mortality was high in poisoning with monocrotophos and dimethoate (31%) and nil with Malathion. In the Mangalore study methyl parathion was the most common poison consumed. Karalliedde L, Senanayake N. reported Dimethoate, Methamidophos, Malathion, Monocrotophos and fenthion as the common type OPC consumed in Srilanka. In the Kashmir valley Phosphomidan (55%), Malathion (12%) and Dichlorvas (8.5%) were the commonly used OPC compounds for ingestion. In study from Tamilnadu, S.Shivakumar Kumar and K.Raghavan et al of Tamilnadu reported Methyl parathion as the most common form of exposure in their study group.

In this case series the severity of poison was directly proportional to quantity consumed. The study from West Bengal showed there was a correlation between the quantity consumed and the mortality.

CLINICAL CONTRIBUTES

In this case series 93.1 per cent of the cases have the accessibility to have their first aid, first doses of atropine and 2PAM within 2 hours. But these variables did not have significant correlation with the outcome. But the West Bengal workers reported increased mortality among the patients who had increased time interval before initial atropinisation [48]. Murat Sungurb et al in Turkey reported that the CNS symptoms such as depressed mental status, confusion and muscle weakness were the common presentation. Kenneth D.Ketz et.al. from Pittsburg reported neuro psychiatric manifestations, ototoxity, Guillain-Barré [49] –like syndrome and isolated bilateral recurrent laryngeal nerve palsy in OPC poisoning.

CLINICAL SEVERITY (MODIFIED DREISHBACH CRITERIA)

In this case series, all the patients admitted fell into the grade 3 group of clinical severity (n=29) 100%. The reason could be that this centre being a referral unit, complicated cases, warranting specialist treatment, intensive care monitoring, ventilatory support were transferred from primary health centres, district hospitals and private nursing homes. Arup Kumar Kundu (et.al) reported, mild 15 (14%), moderate 55 (50.9%), and severe 32 (29.6%) in his study based on OPC poisoning in sub-urban West Bengal. In that study, the severe grade of poisoning was associated with increased ventilatory support and poor outcome. Similarly, in this case series, clinical severity association with need of ventilatory support and mortality was statistically significant.

LAB CONTRIBUTES

In this study group, the average total WBC count 8,686 cells cubic mm. (SD. 3433). Leukocytosis was also reported in the studies from Turkey and Pittsburg. The liver function tests observed in this study had similar pattern of mild elevation when compared to the study from Murat Sungurb et al in TURKEY. Kenneth D. Ketz, et.al. who documented metabolic acidosis in his study group.

CHOLINESTERASE LEVELS AND ITS SIGNIFICANCE

In this case study, day 1 ChE correlated very well with clinical criteria of Dreisbach. This finding was also observed by Bobba R, Venkataraman, BV, Pais P, Joseph T. et.al. in Bangalore [51]. In contrary to this observation, S.N. Chugh and Navneeth Agarwal, et.al. found no relationship between serum CHE

estimation and severity grading [52]. Sequential post exposure estimations of the ChEs up to 3 days revealed significant rise in the values correlated with substantial clinical improvement. This observation was in par with the study in Bangalore [51].

SERUM AMYLASE

In all 29 patients serum amylase and ultra sonogram of the abdomen was performed in order to identify transient pancreatitis which is a rare complication [53]. Ultra sonography of the abdomen was done in all the cases. All cases in our series had serum amylase levels of less than 200. Sahin I, Onbasi K, Sahin H, Karakaya C, Ustun Y, Noyan T. et.al. observed 4 out of 47 cases in their series, had amylase elevation more than 300 U/L.[54]. Lee WC, Yang CC, Deng JF, Wu ML, Ger J, Lin HC, Chang FY, Lee SD, et.al. stated that, hyperamylasemia was frequent in severe organophosphate poisoning. However, hyperamylasemia was not synonymous with acute pancreatitis and pancreatic amylase was not a reliable parameter in the diagnosis of organophosphate-induced pancreatitis due to its low sensitivity and specificity [55].

TREATMENT CONTRIBUTES

In this series, all patients were administered atropine according to the clinical severity.

In this series, 2PAM was given to all patients. 2PAM was administered at a dose of 500 mg/hr infusion for the first 48 hrs followed by 1 g IV tds for another 3 days. Arun Kumar Kundu, et.al. in a study in sub-urban West Bengal

related high dose 2PAM administered in first 24 hours was associated with adverse outcome [48]. In 1991, De Silva studied the treatment of organophosphate poisoning with atropine and 2-PAM and, later the same year, with atropine alone. He found that atropine seemed to be as effective as atropine plus 2-PAM in the treatment of acute organophosphate poisoning. The controversy continued when other authors observed more respiratory complications and higher mortality rates with use of high-dose 2-PAM. Studies are underway to assess the role of low-dose 2-PAM [42] S.Shivakumar and K. Raghavan, et.al. compared the effectiveness of high dose 2PAM with low dose by selection of patients in non-random manner. They found out the high dose 2PAM group had better survival, lesser incidence of type 2 paralysis and shortened duration of ventilation.

VENTILATORY SUPPORT

Out of 29 patients 21 needed ventilatory support. (72.4%).All patients were initiated on assist control mode. 5 out of 21 cases on mechanical ventilation expired. The morality rate among patients on mechanical ventilation was 23.8%.

The average duration of mechanical ventilation in the series was 9.2 days (SD = 6.56). Grade 3 clinical severity, proximal muscle affection, elevation of creatinine Kinase and low values of day 1 serum ChE were the predictors for the need of mechanical ventilation. Murat Sungur and Muhammed Güven of Turkey in the study of 47 patients of OPC reported mechanical ventilatory support was needed for 10 (21.2%) patients. The duration of mechanical ventilation was 4.1 ± 3.2 days. The mortality rate for

the patients who were mechanically ventilated was 50% (5 patients), although the mortality rate was 27.6% (13 patients) for all patients. The mortality rate for the mechanically ventilated patients was not statistically different compared with those patients not mechanically ventilated. Two patients who are mechanically ventilated died with sudden cardio respiratory arrest following ventricular tachycardia, and three died from pneumonia and complicating adult respiratory distress syndrome S.Shivakumar and K. Raghavan, et.al. in their case series of 165 patients 22 to patients were mechanical ventilated, out of which 14 died.

NERVE CONDUCTION STUDIES

All patients underwent nerve conduction studies in the third or fourth week of hospital stay according to the clinical severity. In the nerve conduction study, compound muscle action potential, sensory nerve action potential and nerve conduction velocities were measured in all four limbs. The normal values of these parameters were taken as controls. Thirteen patients had evidence of OPIDP. Three patients had evidence of significant axonopathy, 6 patients had evidence of demyelination and 8 patients had evidence of sensory neuropathy. One patient had evidence of axonopathy, demyelination and sensory neuropathy and two patients had evidence of axonopathy and sensory neuropathy. One patient had evidence of demyelination and sensory neuropathy. Five patients had evidence of demyelination alone and four patients had evidence of sensory neuropathy alone. All Patients with axonopathy also had evidence of either demyelination or sensory neuropathy or both.

One patient developed axonopathy, demyelination and sensory neuropathy after ingesting 200 ml Dimethoate. Of the patients who had axonopathy and sensory neuropathy, one had ingested 100 ml dimethoate and the other had ingested 100 ml monocrotophos.

OUTCOME ANALYSIS

In this series 5 expired. The mortality rate was 17.2%. In all cases primary cause of death was respiratory failure with secondary cardiac arrest. It has resulted from central respiratory depression, respiratory muscle weakness, increased bronchial secretions, broncho spasm and acute pulmonary oedema. The prolonged duration of hospital stay, grade 3 clinical severities, proximal muscle involvement and mechanical ventilation were associated with poor outcome. Karalliedde L, Senanayake N. et.al. reported mortality rate of 18% in their study of 92 cases of OPC in Sri Lanka. Arup Kumar Kundu, JD Mukhopadhyay, AK Saha, S Das Burdwan Medical College and Hospital, Burdwan, West Bengal analyzed that increased time interval before initial atropinisation, higher clinical grading, respiratory paralysis at the time of admission, higher quantity of poison consumed, type of poison (e.g., monocrotophos and dimethoate), poison ingested rather than inhaled, development of encephalopathy and/or is ECG changes (pulse rate < 45/min, complete heart block QT-prolongation), and higher dosage of PAM used in first 24 hours were associated with increased mortality. In Kashmir valley a study of 164 patients of OPC poisoning, the mortality rate was 5.5%. In the Mangalore study, the mortality was 26.2%. Murat Sungur and Muhammed Güven of Turkey reported the mortality rate of 32%.

CONCLUSIONS

- Organophosphorous poisoning is most prevalent in the 21-30 age group. Incidence is more common in males.
- Organophosphorous poisoning is more common among agricultural labourers and unskilled workers.
- The most important cause for consumption of organophosphorous poison is self harm.
- The common route of exposure is ingestion of poison and it is associated with clinical severity.
- The quantity consumed has direct proportional relationship with severity of poisoning
- The duration of stay in the hospital has significant correlation with clinical severity
- The higher the clinical grade of poisoning at initial presentation more the need of ventilatory support and adverse the outcome
- The following parameters predict the need of ventilatory support, grade 3 clinical severity, proximal muscle affection, low values of day 1 serum cholinesterase.
- Ingestion of OPCs produced abnormalities in Nerve Conduction Studies in the form of axonopathy, sensory neuropathy and demyelination

- Ingestion of Monocrotophos produced death in three patients and neuropathy in remaining patients.

- Ingestion of Dimethoate produced all the three abnormalities in NCS

- Ingestion of Monocrotophos caused axonopathy and sensory neuropathy

AREAS OF FUTURE RESEARCH

3. Nerve conduction studies may be done on day 1, 3rd week and 6th month in order to rule out any pre existing polyneuropathy, to identify OPIDP and study its course, respectively.

4. Repetitive nerve stimulation studies may be done daily for the first week to identify intermediate syndrome early

5. Electromyography may be done.

RECOMMENDATIONS

As there is no effective treatment for OPIDP, the only way of prevention is avoiding the exposure to OPCs.

To avoid accidental exposure while spraying pesticides, proper precautions should be taken to prevent inhalation and accidental ingestion of the substance.

Insecticides should be kept out of reach of children, to prevent accidental poisoning.

Improved regulation of the availability of pesticides, strict regulation of vendors, and modifications in packaging of pesticides may all help reduce the use of organophosphates as poisons.

Adequate provision of information to the public creates awareness about the deleterious effects of OPCs.

Establishment of poison information centers will facilitate in reducing the morbidity and mortality related to organophosphorous poisoning.

Many countries like USA, European Union, Thailand banned the production and sales of highly toxic OPCs like Monocrotophos. In Srilanka severe restrictions are enforced over the utilization of Monocrotophos. So the government of India should take necessary steps to restrict the free availability of highly toxic OPCs like monocrotophos.

SUMMARY

Organophosphorous poisoning is a menace to the human race both as a weapon of mass destruction and a misused pesticide of self harm. The case fatality rate exceeds 60% in developing countries where there are many pit falls in treatment protocol and research activities. So a comprehensive analysis of 29 patients of organophosphorous poisoning was done in Poison Centre, Government General hospital Chennai.

All the cases included in the studied underwent detailed clinical evaluation, extensive laboratory work up and nerve conduction studies. Each patient was monitored periodically till the outcome. There were 24 males and 5 female patients. The predominant age group was 21- 30years. 28 patients were suicide attempts and 1 had accidental exposure. 27 of the patients were poisoned through the gastrointestinal route. One patient had inhalational poisoning and one patient had topical exposure. There were 9 different types of OP insecticide agents involved. According to Dreisbach clinical criteria at admission, all patients belong to the severe grade of poisoning. Serum cholinesterase levels had significant correlation with clinical severity, mechanical ventilation and outcome.

Nerve conduction studies were done on the third or fourth week of hospital stay. Both upper and lower limb nerves were studied. Thirteen patients had evidence of OPIDP. Three patients had evidence of significant axonopathy, 6 patients had evidence of demyelination and 8 patients had evidence of sensory neuropathy.

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PROFORMA

ANALYSIS OF ORGANOPHOSPHOROUS POISONING

NAME :

AGE :

SEX :

OCCUPATION:

ADDRESS:

CONTACT NO:

D.O.A D.O.D

DURATION OF STAY:

OUTCOME:

HISTORY

Type of poison

Route of exposure

Ingestional

Topical

Inhalational

Quantity

Time of onset of poisoning

Time of initiation of first aid (lavage activated charcoal)

Time of initiation of atropine

Time of initiation of P2AM

Time taken to reach hospital

Associated poisoning

Associated alcohol intake

Symptomatology

Nausea, vomiting in case of ingestion

Cough, burning sensation in the chest in case of inhalation

Mild systemic symptoms like headache, dizziness, weakness

Abdominal pain, diarrhea in case of ingestion.

Tightness in chest, difficulty in breathing in case of inhalation

Salivation, Lacrimation, Sweating,

Pupillary changes.

Bradycardia,

Confusion, Tremor, Restlessness.

Respiratory depression, generalized weakness

Cyanosis, peripheral circulatory failure,

Convulsions, Coma.

Intention of the poison:

Suicidal

Accidental

Homicidal

Clinical contributes

Mild	No Symptoms; Normal Vitals, Normal Pupils
Moderate	Fasciculation; Perspiration, Pupillary changes; Tachypnoea; Early pulmonary edema
Severe	Pin point pupil, frank pulm-edema, respiratory paralysis, unconsciousness
	Proximal muscle weakness:
	Bulbar muscle weakness:
	Neck weakness:

INTERMEDIATE SYNDROME

Associated Clinical Findings:

LAB CONTRIBUTES

Hemogram:

HB TC DC ESR PCV

RFT

Urea Creatinine Na+ k+ hco3 Cl-

SUGAR :

CXR:

USG Abdomen:

ECG:

Gastric aspirate

Serum pseudo cholineestrase levels

DAY1
DAY2
DAY3

LFT:

SGPT SGOT SAP TB

Amylase:

TREATMENT CONTRIBUTES

Antidote

Ventilatory support

Duration

Tracheostomy

Outcome

Other supportives

- Blood products
- Inotropes
- Dialysis

Nerve conduction studies

- CMAP
- MNCV
- F min
- SNAP