CHAPTER I

INTRODUCTION

Organophosphates are used as insecticides, medications, and nerve agents Symptoms include increased saliva and tear production, diarrhea, vomiting, small pupils, sweating, muscle tremors, and confusion. While onset of symptoms is often within minutes to hours, some symptoms can take weeks to appear. Symptoms can last for days to weeks[2].

Organophosphate poisoning occurs most commonly as a suicide attempt in farming areas of the developing world and less commonly by accident Exposure can be from drinking, breathing in the vapors, or skin exposure. The underlying mechanism involves the inhibition of acetylcholinesterase, leading to the buildup of acetylcholine in the body. Diagnosis is typically based on the symptoms and can be confirmed by measuring butyrylcholinesterase activity in the blood. Carbamate poisoningcan present similarly[2].

Preventive measures include banning very toxic types of organophosphates. Among those who work with pesticides the use of protective clothing and showering before going home is also useful. In those who have organophosphate poisoning the primary treatments are atropine, oximes such as pralidoxime, and diazepam. General measures such as oxygen and intravenous fluids are also recommended. Attempts to decontaminate the stomach, with activated charcoal or other means, has not been shown to be useful. While there is a theoretical risk of health care workers taking care of a poisoned person becoming poisoned themselves, the degree of risk appears to be very small[2].

Organophosphates are one of the most common causes of poisoning worldwide. There are nearly 3 million poisonings per year resulting in two hundred thousand deaths. Around 15% of people who are poisoned die as a result. Organophosphate poisoning has been reported at least since 1962[7].

The symptoms of organophosphate poisoning include muscle weakness, fatigue, muscle cramps, fasciculation, and paralysis. Other symptoms include hypertension, and hypoglycemia. Overstimulation of nicotinic acetylcholine receptors in the central nervous system, due to

accumulation of Acetyl choline, results in anxiety, headache, convulsions, ataxia, depression of respiration and circulation, tremor, general weakness, and potentially coma. When there is expression of muscarinic overstimulation due to excess acetylcholine at muscarinic acetylcholine receptors symptoms of visual disturbances, tightness in chest, wheezing due to bronchoconstriction, increased bronchial secretions, increased salivation, lacrimation, sweating, peristalsis, and urination can occur[8][9].

The effects of organophosphate poisoning on muscarinic receptors are recalled using the mnemonic SLUDGEM (salivation, lacrimation, urination, defecation, gastrointestinal motility, emesis, miosis) An additional mnemonic is MUDDLES: miosis, urination, diarrhea, diaphoresis, lacrimation, excitation, and salivation. The onset and severity of symptoms, whether acute or chronic, depends upon the specific chemical, the route of exposure (skin, lungs, or GI tract), the dose, and the individual's ability to degrade the compound, which the PON1 enzyme level will affect[7].

Certain reproductive effects in fertility, growth, and development for males and females have been linked specifically to Organo phosphorus pesticide exposure. Most of the research on reproductive effects has been conducted on farmers working with pesticides and insecticides in rural areas. For those males exposed to organophosphorus pesticides, poor semen and sperm quality have been seen, including reduced seminal volume and percentage motility, as well as a decrease in sperm count per ejacuate. In females menstrual cycle disturbances, longer pregnancies, spontaneous abortions, stillbirths, and some developmental effects in offspring have been linked to Organo phosphorus pesticide exposure. Prenatal exposure has been linked to impaired fetal growth and development. The effects of Organo phosphorus exposure on infants and children are at this time currently being researched to come to a conclusive finding._Evidence of Organo phosphorus exposure in pregnant mothers are linked to several health effects in the fetus. Some of these effects include delayed mental development, Pervasive developmental disorder , morphological abnormalities in the cerebral surface[4]

Neurotoxic effects have also been linked to poisoning with Organo phosphorus pesticides causing four neurotoxic effects in humans cholinergic syndrome, intermediate syndrome, organophosphateinduced delayed polyneuropathy, and chronic organophosphate-induced neuropsychiatric disorder. These syndromes result after acute and chronic exposure to Organo phosphorus pesticides[5].

Cholinergic syndrome occurs in acute poisonings with Organo phosphorus pesticides and is directly related to levels of acetylcholine activity[1]. Symptoms include miosis, sweating, lacrimation, gastrointestinal symptoms, respiratory difficulties, shortness of breath, slowed heart rate, cyanosis, vomiting, diarrhea, trouble sleeping, as well as other symptoms. Along with these central effects can be seen and finally seizures, convulsions, coma, respiratory failure. If the person survives the first day of poisoning, personality changes can occur, in addition to aggressive behavior, psychotic episodes, memory and attention disturbances, and other delayed effects. When death occurs, it is most commonly due to respiratory failure due to paralysis of respiratory muscles and depression of central nervous system, which is responsible for respiration. For people afflicted with cholinergic syndrome, atropine sulfate combined with an oxime is used to combat the effects of the acute organophosphorous poisoning. Diazepam is sometimes also administered[9].

The intermediate syndrome appears in the interval between the end of the cholinergic crisis and the onset of organophosphateinduced delayed polyneuropathy. Symptoms associated with intermediate syndrome manifest between 24–96 hours after exposure. The exact etiology, incidence, and risk factors associated with intermediate syndrome are not well understood, but intermediate syndrome is recognized as a disorder of neuromuscular junctions. Intermediate syndrome occurs when a person has a prolonged and severe inhibition of acetylcholine. It has been linked to specific Organo phosphorus pesticides such as parathion, methylparathion, and dichlorvos. Patients generally present with increasing weakness in the facial, neck flexor, and respiratory muscles.[2]

Organophosphateinduced delayed polyneuropathy occurs in a small percentage of cases, roughly two weeks after exposure, where temporary paralysis occurs. This loss of function and ataxia of peripheral nerves and spinal cord is the phenomenon of organophosphateinduced delayed polyneuropathy. Once the symptoms begin with shooting pains in both legs, the symptoms continue to worsen for 3–6 months. In the most severe cases quadriplegia has been observed. Treatment only affects sensory nerves, not motor neurons which may permanently lose function. The aging and phosphorylation of more than 70% of functional NTE in peripheral nerves is one of the processes involved in organophosphateinduced delayed polyneuropathy. Standard treatments for Organo phosphorus poisoning are ineffective for organophosphateinduced delayed polyneuropathy[1].

Chronic organo phosphate-induced neuropsychiatric disorder occurs without cholinergic symptoms

and is independent of acetylcholine esterase inhibition. Chronic organo phosphate-induced neuropsychiatric disorder appears with a delay and is long lasting. Symptoms associated with Chronic organo phosphate-induced neuropsychiatric disorder include cognitive deficit, mood changes, autonomic dysfunction, peripheral neuropathy, and extrapyramidal symptoms. The underlying mechanisms of Chronic organo phosphate-induced neuropsychiatric disorder have not been determined, but it is hypothesized that withdrawal of organo phosphorous pesticides after chronic exposure or acute exposure could be a factor.

CHAPTER II

LITERATURE REVIEW

MK Johnson (1975) "Organophosphorus esters causing delayed neurotoxic effects" - Explained that Evidence is reviewed that the initial biochemical event leading to delayed neurotoxicity is phosphorylation of the active site of a specific enzyme called Neurotoxic Esterase. This is followed by a bondcleavage leading to formation of a monosubstituted phosphoric acid residue on the protein. The mechanism by which some phosphinates protect hens against neurotoxic compounds. In Screening Assay, effects of compounds on Neurotoxic Esterase activity of hen brain in vitro and in vivo provides a quick biochemical screen to supplement the 3-week clinical test. This test provides an estimate of safety margin for compounds which give negative results in the clinical test and are currently used as pesticides, plasticisers, etc. Simplified assay procedures are being developed.

Kathleen C Raffaele, et al. (2010) "The use of developmental neurotoxicity data in pesticide risk assessments" - Explained the passage of the Food Quality Protection Act, which mandated an increased focus on evaluating the potential toxicity of pesticides to children, the number of guideline developmental neurotoxicity studies submitted to the U.S. Environmental Protection Agency Office of Pesticide Programs was greatly increased. To evaluate the impact of available studies on individual chemical risk assessments, the ways in which data from these studies are being used in pesticide risk assessment.

William F Sette, 1989, in "Adoption of New Guidelines and Data Requirements for More Extensive Neurotoxicity Testing under Fifra,"- In 1987 the Center for Science in the Public Interest and others petitioned to, "issue testing methods necessary to fully assess the neurotoxic and neurobehavioral effects of pesticide active and inert ingredients. " In response Organo phosphorous poisoning convened a meeting of an expert subpanel on neurotoxicity of the Scientific Advisory Panel to review its proposed response. The petitioners proposed specifically that Organo phosphorous poisoning use the neurotoxicity guidelines developed by United States Environmental Protection Agency own Office of Toxic Substances. They asserted that the scope of potential neurotoxic hazards is broad and that current guidelines will neither adequately identify nor characterize these effects. A series of expert panels have endorsed the use of more extensive neuropathological evaluations, better clinical examinations, explicit unconditioned and conditioned

behavioral testing, testing of prenatally exposed animals for neurological deficits, and development of a means for evaluation of the broad range of potential neurotoxic effects.

Kerry L Dearfie, et.al, (1999), "A survey of United States Environmental Protection Agency and open literature on selected pesticide chemicals: II. Mutagenicity and carcinogenicity of selected chloroacetanilides and related compounds" explained With this effort, we continue our examination of data on selected pesticide chemicals and their related analogues that have been presented to the U.S. Environmental Protection Agency's Office of Pesticide Programs. This report focuses on a group of selected chloroacetanilides and a few related compounds. As part of the registration process for pesticidal chemicals, interested parties must submit toxicity information to support the registration including both mutagenicity and carcinogenicity data.

Marina Bjørling-Poulsen, et.al ,(2008), in "Potential developmental neurotoxicity of pesticides used in Europe" - explained Pesticides use in agriculture are designed to protect crops against unwanted species, such as weeds, insects, and fungus. Many compounds target the nervous system of insect pests. Because of the similarity in brain biochemistry, such pesticides may also be neurotoxic to humans. Concerns have been raised that the developing brain may be particularly vulnerable to adverse effects of neurotoxic pesticides. Current requirements for safety testing do not include developmental neurotoxicity. We therefore undertook a systematic evaluation of published evidence on neurotoxicity of pesticides in current use, with specific emphasis on risks during early development. Epidemiologic studies show associations with neurodevelopmental deficits, but mainly deal with mixed exposures to pesticides.

Robin Mesnage, et.al, 2015, in "Potential toxic effects of glyphosate and its commercial formulations below regulatory limits" - explained Glyphosate-based herbicides, including Roundup, are the most widely used pesticides worldwide. Their uses have increased exponentially since their introduction on the market. Residue levels in food or water, as well as human exposures, are escalating. We have reviewed the toxic effects of Glyphosate-based herbicides measured below regulatory limits by evaluating the published literature and regulatory reports. We reveal a coherent body of evidence indicating that Glyphosate-based herbicides could be toxic below the regulatory lowest observed adverse effect level for chronic toxic effects. It includes teratogenic, tumorigenic and hepatorenal effects.

Susan L Makris, et.al, (2009) "A retrospective performance assessment of the developmental

neurotoxicity study in support of test guideline 426" - explained review of the history and performance of developmental neurotoxicity testing in support of the finalization and implementation of Organisation of Economic Co-operation and Developmental Neuro Toxicity test guideline. In this review we summarize extensive scientific efforts that form the foundation for this testing paradigm, including basic neurotoxicology research, interlaboratory collaborative studies, expert workshops, and validation studies.

Wolfgang Kaufmann (2003) "Current status of developmental neurotoxicity: an industry perspective"- explained the chemical industry, along with the rest of society, shares the fundamental goal to protect the health and safety of children. Most of the existing testing programs for environmental chemicals primarily address the adult organism. Developmental neurotoxicity testing studies are especially designed to address the specific risks of the developing nervous system. At time, Developmental neurotoxicity studies are not a regulatory requirement for all pesticides.

Sven W Sauer, et.al, (2010) "Molecular Basis of Disease" - Glutaric aciduria type I and methylmalonic aciduria: simulation of cerebral import and export of accumulating neurotoxic dicarboxylic acids in in vitro models of the blood" explained Intracerebral accumulation of neurotoxic dicarboxylic acids plays an important pathophysiological role in glutaric aciduria type I and methylmalonic aciduria. Therefore, we investigated the transport characteristics of accumulating dicarboxylic acids – glutaric, 3hydroxyglutaric and methylmalonic acid – across porcine brain capillary endothelial cells and human choroid plexus epithelial cells representing in vitro models of the blood–brain barrier and the choroid plexus respectively.

Robin Mesnage, et.al (2015) "Potential toxic effects of glyphosate and its commercial formulations below regulatory limits" - explained Glyphosate-based herbicides, including Roundup, are the most widely used pesticides worldwide. Their uses have increased exponentially since their introduction on the market. Residue levels in food or water, as well as human exposures, are escalating. We have reviewed the toxic effects of Glyphosate-based herbicides measured below regulatory limits by evaluating the published literature and regulatory reports. We reveal a coherent body of evidence indicating that Glyphosate-based herbicides could be toxic below the regulatory lowest observed adverse effect level for chronic toxic effects. It includes teratogenic, tumorigenic and hepatorenal effects.

CHAPTER III

AIM AND OBJECTIVES

AIM:-

To identify the Neurological Responses initially and identifying the dosage of fatality ,symptoms exhibited due to organo phosphorous pesticide ingestion and methods of treating patients with antidotes.

OBJECTIVES:

- Site of Action of organophosphorous in the human body
- Signs and symptoms after a organophosphorous pesticide enters the body
- Treating patients accordingly to the concentration and amount of pesticide intake

CHAPTER IV

MATERIALS AND METHODOLOGY

Material Required:

The mainstays of medical therapy in organophosphates poisoning include atropine, pralidoxime(2-PAM), and benzodiazepines. Initial management must focus on adequate use of atropine.

Methodology:

Identification of Pesticide : Identified pesticide at admission to know patients at risk of developing respiratory failure. Monocrotophos, Diamethoate present with early and rapid onset of respiratory paralysis within few hours of ingestion. Identify pesticide by history given by patient, container of pesticide and clinical presentation. Ask patient to identify pesticide by showing photographs. World Health Organisation colour code on container can also give clue. Monocrotophos, class I toxic pesticides available in local market. The patients having signs of cholinergic excess or developing intermediate syndrome are also cases of Organophosphorus poisoning. In case of disparity between history and clinical presentation, follow your clinical judgment. After identification of pesticide classify it as Organophosphorus and non-Organophosphorus for further treatment.

Measured pulse rate and blood pressure and auscultate the lungs. Placed patient in the left lateral position- head lower than the feet. Started 60% oxygen. Started atropine quickly to reduce bronchorrhoea responsible for respiratory distress. Did a Set up an infusion of 0.9% normal saline. The systolic blood pressure > 80 mm Hg and urine output >30 ml/h . Injected 0.6- 1 mg IV atropine. The pulse rate does not goes up by 25 per minute or skin flushing did not developed hence patient has mild or no toxicity. Checked three things after five minutes: pulse, blood pressure and chest crackles. The heart rate >80 beats per minute, SBP > 80 mm Hg, and a clear chest (atropine won't dry focal areas of aspiration). Reviewed patient every 5 min. Once these

parameters started improving, repeated last same or smaller dose of atropine.The improvement in these parameters is persistent and satisfactory after 5 min,hence did atropine infusion. Atropine infusion Calculated total dose of atropine required for rapid atropinisation. Started hourly atropine infusion at 20% of total dose of atropine required for atropinisation. Caution Most patients do not need >3-5 mg (5-9 ml) per hour of atropine infusion. Used three-point checklist to reduce infusion rate by 20% every 4 hourly once patient was stable did not use oral secretions to guide therapy in patients who are intubated, unconscious, having oropharyngeal airway in situ and with intermediate syndrome. Ignored sweating to adjust atropine dose. Stable Patients with clear chest but heart rate just below target did not need further more atropine. Bronchorrhoea was found the most important sign for titrating dose of atropine once patient was stable. Atropine toxicity lead to absent bowel sounds, fever and confusion. Stopped atropine infusion for 60 min, because patient might have developed atropine toxicity. Re-started infusion at 80% of initial rate, once the temperature came down and the patient got calm. Only to treat Organophosphorus poisoned patients. There was no evidence that oximes were a useful treatment for organophosphate pesticide poisoning . Bolus dose: 45 mg/kg Pulse Amplitude Modulation over 30 minutes. Maintenance dose was continuous infusion of 12 mg/kg per hour. Pulse Amplitude Modulation for a 50-kg person: 2 g (bolus) and 600 mg per hour. PAM must be given by Infusion. We had to go slow, both for bolus and maintenance. A fast infusion might have caused vomiting, hypertension, cardiac arrhythmia or a cardiac arrest. Then we had to stop giving Pulse Amplitude Modulation until atropine was no longer required. Sedation and anticonvulsant Agitation and seizures diazepam 10 mg slow IV push, repeated as necessary. Up to 3040 mg diazepam per 24 hours had given. Used diazepam infusion for status epilepticus. Given general anesthetic agents (propofol, midazolam) because seizures were not controlled by diazepam. Gastric lavage and decontamination took place .Considered lavage because the patient might have taken a large amount of highly toxicpesticide. The patient reached hospital within 1-2 hours. Checked whether the patient is conscious, cooperative or is intubated. Larger volumes (>300ml) of lavage fluid might have pushed the poison into the intestine. Washed the body because skin might have exposed to the pesticide. Did not use activated charcoal Weaning off ventilator. Patients developed respiratory failure in intermediate syndrome because of respiratory muscle weakness. There was respiratory muscle performance before weaning off patient from mechanical ventilator. Maximum voluntary ventilation was >20 L/min Respiratory frequency 6 breaths/min To wean off, reduced slowly and

gradually pressure support level in Continuous Positive Airway Pressure with Pressure Support Ventilation mode. Extubated because the patient might have been breathing spontaneously with no distress and generated tidal volume>5 mL/kg at pressure support of 35 cm of H2O. Intermediate syndrome, it usually found 12 to 96 hours after exposure Early signs of intermediate syndrome were action tremors and pharyngeal weakness (difficulty in deglutition or pooling of secretions in pharynx). Later patient developed inability to flex neck, deep tendon jerks were lost and developed cranial neuropathies, proximal muscle weakness and respiratory muscle paralysis. Not all patients developed the full intermediate syndrome that required intubation and ventilation, but patients with tremors and pharyngeal weakness were at risk. Alcohol intoxicated patients were usually aggressive and abusive and calmed down within 12 hours of arrival. Patients with atropine toxicity had fever, muttering, delirium, absent bowel sounds, full bladder and dilated pupil. Altered sensorium should be attributed to pesticide because these signs were absent and patient continued to be disoriented or confused after 12 hours of arrival. It was also one of the early signs of intermediate syndrome. Treatment of intermediate syndrome was totally symptomatic. Patient required ventilator support because he developed respiratory muscle paralysis. Did not use atropine because signs of cholinergic excess were absent.

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CASE REPORT:-

1. A student, aged 22 years, (male) was admitted in neuro ICU with an episode of seizure and altered sensorium. He had no premorbid illness. He had travelled to Chennai three days before admission. Relatives denied consumption of any poison and medications. At the time of hospitalization, he was restless and was in postictal state. Vital signs revealed pulse rate of 62/minute, blood pressure of 120/80 mmHg, respiratory rate of 14 per minute, afebrile, and had plenty of oral secretions. Neurological examination revealed GCS of 6/15 with reduced movements of all four limbs. Pupils were pin point bilaterally with absent Doll's eye movement. Plantar reflex was extensor bilaterally. Deep tendon reflexes were sluggish. There were no fasciculation and no smell of Organo phosphorous compound. He had cellulitis of left arm. Examination of chest showed bilateral crepitations. Examination of other systems was normal. Investigations at admission showed normal renal functions, liver functions, and normal serum levels of sodium, potassium, calcium, and magnesium. Blood picture showed leukocytosis. Chest X-ray showed bilateral haziness suggesting acute respiratory distress syndrome. Ultrasonography of left arm showed pus collection in the intramuscular plane. Debridement was done and 250 ml of pus was drained. At this point of time, differential diagnosis of metabolic encephalopathy, toxic encephalopathy due to sepsis, possible brain stem diseases, and Organo phosphorous poisoning/drug over dosage were considered. Computed tomography and magnetic resonance imaging scan of the brain, lumbar puncture and CSF analysis were done and they were normal. His EKG, cardiac enzymes, and echocardiography were normal and blood, urine, and pus cultures were sterile. Screening for benzodiazepine, antiepileptic drugs were negative. Serum cholinesterase level was 1234 units (reference range- 5000 – 9000 units). On day 2, he developed respiratory distress with carbon dioxide retention, ABG revealed $PaCO_2$ of 54 mmHg, and he required ventilator support. At this point of time, we had reasonably excluded metabolic and structural causes for his problem; hence, possibility of Organo phosphorous poisoning was considered on the basis of respiratory failure, pulmonary secretions, supported by low plasma cholinesterase level. Ryle's tube aspiration was done at the time of hospitalization and gastric aspirate was minimal. Empirically, he was treated

with atropine and pralidoxime along with broad spectrum antibiotics. Atropine was given 5 mg bolus, followed by infusion at the rate of 2 mg/h, and the dose was titrated as per his clinical response and signs of atropinisation. Response to atropine treatment was good and over five days gradual improvement in sensorium was noticed. Pralidoxime was given at a dose of 1 gm infusion, three times per day for initial two days. He was treated with phenytoin sodium for seizures. Initial antibiotics were piperacillin-tazobactam and metronidazole but during the course of illness, there were worsening of chest shadows and antibiotics were changed to meropenem and linezolid. Cultures of endotracheal tube secretions were sterile. His chest X- ray and oxygenation improved. In the initial three to four days, fluctuation in the sensorium was noticed but continued to have neuroparalysis, neck muscle weakness, and his respiratory efforts were poor. His restlessness was controlled with diazepam. He continued to require ventilator support for breathing. We kept talking to relatives regarding possible consumption of OP poison, but they had no clue about any such event. Plasma cholinesterase level was repeated and value had gone down to 934 units. His restlessness was better, became more alert and neuroparalysis started recovering slowly. The entire problem got sorted out on sixth day, when he communicated to us in writing that he had injected metacid (methyl parathion) to his left arm while travelling in train. He required ventilator support for 12 days and recovered completely. He revealed that he had injected poison with suicidal intention and all the legal protocols were done as per the hospital rules. Following recovery, he was evaluated by psychiatrists and revealed that injection of poison was an impulsive act due to poor social and financial support from family.

2. A 24 year old male patient was admitted in medical ward with history of ingestion of parathion the patient has vomited immediately after ingestion of parathion. There was history of drowsy, poorly responding oral commands, patient was unconscious. Clinical examination was normal Investigation showed serum urea is 15 mg/dl and serum creatinine 0.9 mg/dl, total serum bilirubin was 1.5 mg/dl and conjugated was 1.9 mg/dl. The transaminases were SGOT- 39 IU and SGPT- 42 IU, temperature was normal, pulse rate 110/min., heart rate 120/min., and RR 12/min. Blood pressure were 110/80 mm hg the patient was managed with in on 45 days. Patient was on oxygen support 2 lit/ml. Through nasal prongs, patient was on continuous cardiac monitoring, mechanical ventilator support done for 13 days than he could be successfully weaned. Atropine and pralidoxime has been

continued. The patient was conscious but not oriented, continuous cardiac monitoring gentile chest percussion and vibration given, followed by suction. There after the patient was stable, transfer in general ward the patient will be cured with in on 45 days.

CHAPTER V

CONCLUSION

Organophosphorous compound toxicity by parenteral route is a diagnostic challenge. Onset of symptoms may be delayed and presentations may be atypical. Even though the symptoms are mild initially, observation for longer period is required. As there are no decontaminating measures, even a small quantity of injection may be fatal. The treating physicians should be vigilant, and appropriate treatment has to be administered in the event of suspicion of Organophosphorous. Organophosphate poisoning is a common and acute problem in leading country because of due to easily available of pesticide. Young adult should be educated about poisoning hazards and should be aware about the poisoning. Clinical and health care professional should be provide technique in rural place, how to prevent and also give some tips about emergency condition.

CHAPTER VI

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