

How to Cite:

Kumar, K. R., & Sinha, S. N. (2022). A review of the clinical management of current organophosphate poisoning treatments in humans. *International Journal of Health Sciences*, 6(S9), 2394–2415. <https://doi.org/10.53730/ijhs.v6nS9.12950>

A review of the clinical management of current organophosphate poisoning treatments in humans

Kumpati Rajesh Kumar

Division of Food Safety, Indian Council of Medical Research - National Institute of Nutrition, Tarnaka, Hyderabad, 500007, India

Sukesh Narayan Sinha

Scientist-F, Head of Department, Division of Food Safety, Indian Council of Medical Research - National Institute of Nutrition, Tarnaka, Hyderabad, 500007, India

Corresponding author email: sukeshnr_sinha@yahoo.com

Abstract--Although they have several uses, organophosphates (OPs) are mostly employed in agriculture as insecticides. Every year, OPs are too accountable for the deaths of hundreds of thousands of individuals. Acute toxicity is caused by overstimulating the central and autonomic nervous systems with nicotinic and muscarinic receptors, as well as the neuromuscular junction, as a result of acetylcholinesterase (AChE) enzyme suppression. Based on the poisoning history, the odor of pesticides, the distinctive clinical symptoms, and decreased cholinesterase activity are used to make the diagnosis of OP poisoning. The keys to successful outcomes are appropriate supportive care, decontamination, intensive anti-muscarinic therapy, early seizure management, and the administration of antidotal oxime medication.

Keywords--Organophosphate, Pesticides, Chemical Warfare, Pharmacology, Epidemiology, Clinical Management.

1. Introduction

In low-middle income nations, pesticide consumption continues to be a common intentional self-harm that frequently manifests as a medical emergency. Organophosphate (OP) chemicals continue to be the most popular pesticide used for self-poisoning due to its easy accessibility in agricultural communities and rural locations. (Gunnell D et al., 2007; Murray et al., 2002; Senanayake N & Petris H 1995; Eddleston et al., 2022; Singh S et al., 1984; Thomas M et al., 2000). Because of their effectiveness against insects and low toxicity to humans,

OP compounds have seen an upsurge in use since their discovery in the late 1930s. There are many different types of chemicals in this category, some of which are poisonous and are used in chemical warfare. For instance, 96 young male volunteers who had been percutaneously exposed to toxic OP nerve agents in the late 1960s showed evidence of altered awareness and prolonged attention, as well as reduced motor and cerebral processes. (Pereira EFR et al., 2014) Despite the difficulty in establishing the true incidence of organophosphate poisoning due to the difficulties in gathering data for surveillance, it is predicted to result in 250 000 to 350 000 deaths per year globally (Peshin SS et al., 2014; Kir MZ et al., 2013).

For the safe application of pesticides, the Indian government has taken action. The Insecticides Act, which was introduced in India in 1968 and came into effect on August 1, 1971, aims to control the use of insecticides as well as their manufacture, distribution, sale, and use in order to reduce dangers to people and animals. Prior to the Insecticides Act's implementation, it was advisable to assess the extent of the nation's pesticide pollution and the associated health risks in order to assure their safe usage for the good of society. A number of national laboratories, agricultural universities, and other R and D organisations, including the National Institute of Occupational Health (NIOH), Ahmedabad, have been working on the toxicological evaluation of pesticides, the synthesis of safer molecules, and the assessment of environmental contamination brought on by pesticides. In India during the past three decades, both pesticide production and consumption have increased in lockstep. However, India consumes these chemicals differently from the rest of the globe (Mathur 1999). (Table 1).

These substances block acetylcholinesterase (AChE) by alkyl phosphorylating a serine hydroxyl group, which prevents acetylcholine from being hydrolyzed into acetic acid and choline. Abnormally high acetylcholine levels can cause the toxidrome by activating neuronal connections in the neuromuscular junction, central nervous system, and autonomic nervous system if they are not hydrolyzed (Namba T et al., 1971; King Am & Aaron Ck 2015; Henretig Fm et al., 2019). Organophosphates compounds are poisonous when absorbed by the skin, mucosal membranes, or respiratory tract after accidental exposure, or through the digestive tract after suicidal consumption. As part of their metabolic process, esterases hydrolyze them. Although they interact and bind to many different human body enzymes, their effect on the enzyme acetylcholinesterase (AChE) is of therapeutic significance. These substances impair the enzyme's normal function by attaching to the active site of esterase activity on the acetylcholinesterase molecule and phosphorylating it (Koelle GB 1992).

OP primarily target the neurological, respiratory, and cardiovascular systems. OP exposure in humans can happen in a number of ways, including through contaminated food, water, and the environment (Ambali SF & Ayo JO 2011). OPs have been linked to both acute and chronic disorders because it has been demonstrated that they harm a number of tissues, including the brain, kidney, and liver (balali Mood M & Shariat M 1998). Numerous nations, including India, are initiating plans to reduce down on the use of pesticides in conventional agriculture (Abilash P C & Singh N 2009; Mathur H B et al., 2003).

2. History & Composition

Schrader swiftly invented OP compounds for the first time before and during the Time World War. They were initially used as a farmed bug spray before being considered for use as potential chemical fighting personnel. (Taylor P 1996). Nerve operators have clearly emerged as weapons of mass destruction in the late 1990s and early 2000s, as a result of increased attention being paid to psychological warfare. According to the proximity of the coupling covalent carbon to phosphorus (C-P) link, these exacerbates' OPs are a collection of both synthetic and biological OP mixtures. The carbon-phosphorus bond in OPs takes the place of one of the four carbon-to-oxygen-to-phosphorus bonds in the more common phosphate ester. (Wanner BL & Metcalf WW 1992). Even though phosphate ester bonds are present in the vast majority of naturally occurring phosphorus-containing mixtures, phosphonates, both artificially created and naturally occurring, are nevertheless important. (Blackburn GM 1981) Because the initial C-P linkage is synthetically and thermally passive, most organophosphate mixtures are undifferentiated from mixtures containing the more sensitive N-P, S-P, or O-P connections and are hence resistant to concoction hydrolysis, heated disintegration, and photolysis (Fig. 1). Both ethyl and methyl are represented by the letter R (Fig. 2). The sprays of pesticides with two times as much sulphur are toxic to the liver. Phosphonate has the partner alkyl(R-) of one alkoxy group in situ (RO-). The primary metabolite for a specific distinguishing proof is X, often known as leaving gathering.

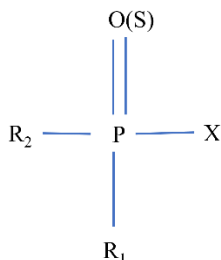


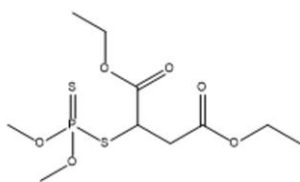
Fig 1: General composition of organophosphorus compounds

Although other chemical alternatives are also available, R1 and R2 are often alkoxy groups.

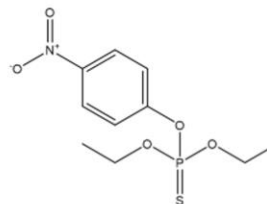
The phosphorous is also connected to the oxygen or the sulphur atom by a double bond.

X, which is more susceptible to hydrolysis, is known as the leaving group, which is exhibited when the OP phosphorylates acetylcholinesterase (AChE).

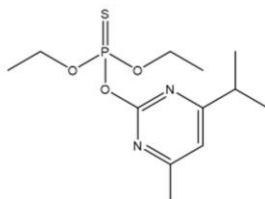
Structure of OP pesticides



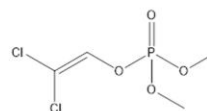
Malathion



Parathion



Diazinon



Dichlorvos

Fig 2: Chemical Structure of some Organophosphorus compounds

Table 1
Top state wise consumption of pesticides in India during the years 2017-2022

S No	State/UTs	Total pesticides consumed (in Metric Tons)
1	Maharashtra	66515
2	Uttar Pradesh	57335
3	Telangana	24751
4	Punjab	21566
5	Haryana	20356
6	West Bengal	17062
7	Rajasthan	11119

Database from Directorate of plant protection, quarantine and storage (<http://ppqs.gov.in/statistical-database>)

3. Epidemiology

Particularly in underdeveloped nations, acute pesticide poisoning is a significant global cause of mortality and morbidity (Kishi M & ladou J 2001). There are no reliable global estimates for pesticide-related health effects due to a number of factors, including a lack of standardized case definition (Thundiyl JG et al., 2008), despite the fact that there is a substantial body of evidence linking pesticide exposure to an increased risk of chronic diseases (Mostafalou S & Abdollahi M 2013). According to studies conducted in developed nations, there are 18.2 acute pesticide poisoning cases for every 100,000 full-time agricultural

workers per year (Calvert GM et al., 2004). In diverse parts of the world, there may be a variety of factors that influence the pattern of acute pesticide poisoning. The most significant contributors to the higher prevalence of acute and chronic pesticide poisonings in developing nations are inadequate regulatory and monitoring systems, weaker enforcement, inadequate training, inadequate public education, a lack of access to poison information and control centers, poorly maintained or nonexistent personal safety equipment, and larger agriculturally based populations (Thundiyil JG et al., 2008).

Pesticide self-poisoning is a significant public health issue in various nations, including China, Pakistan, India, and Sri Lanka (Ather NA et al., 2008; Zhang J et al., 2009; Murali R et al., 2009; SenarathnaL et al., 2012). Other causes of these discrepancies include the use of different recording techniques, underestimating the true prevalence of poisoning, and the absence of a common case definition for acute pesticide poisoning (Thundiyil JG et al., 2008). Measures needed for suicide poisonings are different from those for occupational and unintentional pesticide poisoning. As a result, it's critical to appropriately assess the problem's significance through better estimations, case identification, and death tolls from acute pesticide poisoning. Misdiagnosis by medical experts, the exclusion of outpatients, and the lack of access to healthcare in rural areas are major obstacles to determining the extent of the issue (Alavanja MC et al., 2001).

Additionally, the total occupational/nonintentional incidence of acute pesticide poisoning may be understated by research based on hospital data due to suicidal attempts with pesticides for the most severe poisoning (Litchfield MH 2005). The World Health Organization (WHO) estimates that poisoning leads to about 250,000 deaths worldwide each year, with pesticides accounting for 150,000 of those deaths (WHO Geneva 2020). Lower- and middle-income countries (LMIC) account for the majority of poisoning deaths (Karunaranthne A et al., 2020). The disparity between developing and developed countries in this matter may also be impacted by the fact that many poor countries lack the toxicovigilance programmes and laboratory capabilities required for the confirmation of all suspected acute pesticide poisoning cases (Thundiyil JG et al., 2008).

Numerous variables, including chemical class and identification, dose, route of exposure, formulation type, underlying physiological conditions, comorbidities, coingestion, age, occupation, economic status, and educational attainment, might influence the severity and likelihood of acute pesticide poisoning (Tioco-Ojanguren R & Halperin DC 1998; Oliveira-Silva JJ et al., 2001; Mancini F et al., 2005). OPs are the most popular pesticides used in most nations to safeguard agricultural crops against pests (Kazemi M et al., 2012). Due to their unstable chemical nature, which causes quick hydrolysis and limited long-term environmental accumulation, OPs have grown in popularity for both domestic and agricultural application (Kumar SV et al., 2010). Increased human poisonings, particularly in developing nations, are a result of their widespread usage and accessibility (Pratim Maiti P et al., 2011). There are thought to be over 3,000,000 OP intoxications annually, and more than 80% of them result in hospitalizations for pesticide-related illnesses. An estimate of 20% for the overall fatality rate (Pratim Maiti P et al., 2011).

In 1990, the World Health Organization issued the first global estimates of the amount of pesticide poisoning (WHO). Based on extrapolations from sparse data, it was estimated that 220,000 deaths, mostly from intentional use of pesticides, resulted from 3,000,000 cases of pesticide poisoning worldwide each year (WHO 1990). OPs and other toxic pesticides that are widely available and utilized in agriculture have made pesticides the preferred tool for self-harm (Kumar SV et al., 2010).

4. Pathophysiology

The two cholinergic receptor subtypes that are present in both humans and animals are muscarinic and nicotinic receptors. These receptors are further divided into subgroups based on where they are found in the body and what happens once acetylcholine binds to the receptor. The central nervous system (CNS), exocrine glands, and hollow end-organs innervated by the parasympathetic system all contain muscarinic receptors, while postganglionic neurons of the parasympathetic and sympathetic chains, the adrenal medulla, and the neuromuscular junction all contain nicotinic receptors (Fig. 3) (Katzung BG section II 2004). Both are present in the brain.

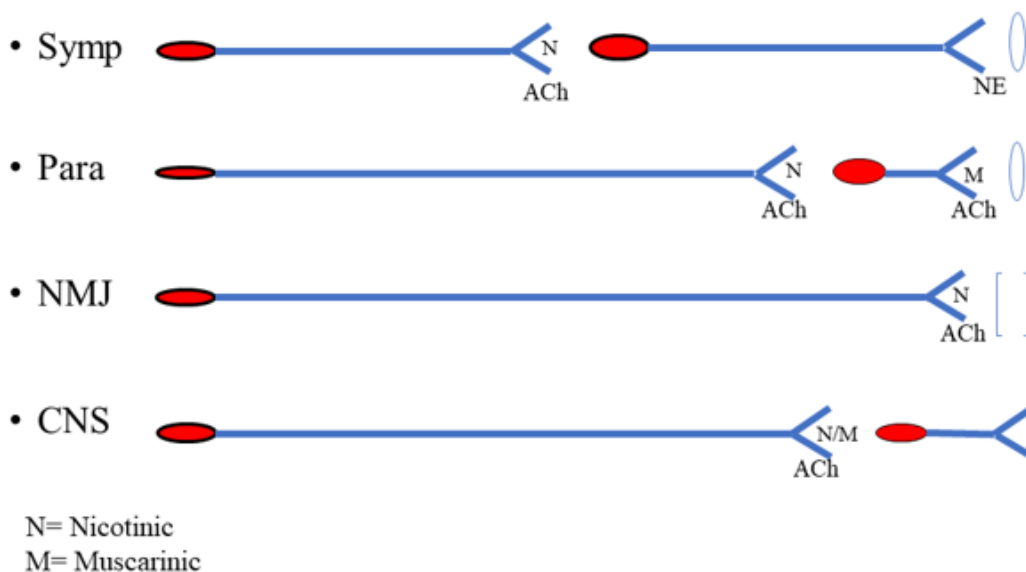


Fig. 3: Synaptic Nerve ending of ANS & CNS

Different end-organ effects are brought on by excess acetylcholine at the two receptor subtypes. Toxicities caused by OP can be principally nicotinic (hypertension, tachycardia, fasciculations, weakness, mydriasis), muscarinic (miosis, bradycardia, bronchospasm, bronchorrhea), or a mixture of the two. Similar to how succinylcholine depolarizes and paralyzes skeletal muscle, excessive acetylcholine at the neuromuscular junction causes type II paralysis. Additionally, cholinergic neurons interact with other neurotransmitter systems to block GABA and activate N-methyl-D-aspartate, which may in part be the cause

of respiratory depression and seizure activity that is mediated by the central nervous system (CNS) (Bird SB et al., 2003; Dickson EW 2003; Dekundy A et al., 2007; Kozhemyakin M et al., 2010). Cholinergic toxicity's clinical symptoms are outlined in Table 2.

Table 2
Clinical symptoms of organophosphate poisoning

S NO	Anatomic site of action	Sign & Symptoms
1	Muscarinic Effects	
	a. Ophthalmic	Blurred Vision, Conjunctival injection, lacrimation
	b. Respiratory	Rhinorrhea, Cough, Excessive Sputum
	c. Cardiovascular	Bradycardia, Hypotension
	d. Dermal	Flushing
	e. Gastro Intestinal	Nausea, vomiting, salivation, diarrhea, abdominal cramping, fecal inconstitence
2.	Nicotinic Effects	
	a. Cardiovascular	Tachycardia, hypertension
	b. Striated Muscle	Fasciculations, Twitching, cramping, weakness, paralysis
3.	Central Nervous system Manifestations	Anxiety, restlessness, depression, confusion, ataxia, tremors, convulsions, coma

5. Toxicology

Acetylcholinesterase (AChE) inhibition at cholinergic synapses throughout the central nervous system and autonomic nervous system, as well as at the neuromuscular junction, is the primary mechanism of OP pesticide toxicity (NMJ). Because acetylcholine cannot be broken down, muscarinic and nicotinic receptors are overstimulated, which causes bronchospasm, bronchorrhea (pulmonary edema), bradycardia and hypotension, neuromuscular Junction dysfunction, and decreased consciousness, among other clinical symptoms. (Lotti M 2001 Vol 2; Eddleston M 2018 11th ed. ; Peter JV et al., 2014).

6. Clinical manifestation

Agent, route, formulation, dosage, and length of exposure are only a few of the variables that affect the toxicity's onset and severity. Inhalational exposure to nerve agents, for instance, can cause death within minutes, whereas skin exposure to highly lipophilic compounds that need activation can cause symptoms to manifest up to 48 hours later (Sakamoto T et al., 1984). Clinical effects are anticipated to start between 30 and 90 minutes after ingesting, with the time to beginning of symptoms generally being slightly delayed compared to inhalation.

The route of exposure also affects the initial and apparent symptoms. Vomiting and other gastrointestinal symptoms are frequently evident with ingestion, whereas ocular and respiratory symptoms are generally present with aerosol exposure. Localized perspiration and fasciculations are possible symptoms of dermal exposure. Exposure can happen during formulation production, mixing, or spraying, and both cutaneous and inhalational exposures are recognised occupational hazards. When employees disregard proper workplace hygiene, it may result in non-suicidal ingestion.

The stimulation of muscarinic and nicotinic receptors results in clinical consequences (see Table 3). Muscarinic stimulation results in diarrhoea, urine, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, and salivation. Nicotinic receptors in the sympathetic ganglia and neuromuscular junction are stimulated, and this results in mydriasis, tachycardia, weakness, hypertension, and fasciculations (Walter FG 3rd ed. 2003). Misdiagnosis is possible as a result of the "mixed" nicotinic and muscarinic clinical effects (Zwiener RJ & Ginsburg CM 1988). More severe poisonings often cause clinical symptoms caused by nicotinic receptor activation to manifest first (Bradberry SM & Vale J 2005).

There are many different CNS impacts that can be both mild and serious. Headache, vertigo, restlessness, anxiety, sleeplessness, disorientation, tremor, dysarthria, ataxia, convulsions, coma, and central respiratory depression are some of these side effects (Asari Y et al., 2004). Finally, it is not unexpected that both acute and delayed extrapyramidal symptoms arise given the necessity for balance between the dopamine and cholinergic systems (Joubert J et al., 1984; Senanayake N & Sanmuganathan PS 1995; Shahar E & Andraws J 2001). Particularly important factors are muscle weakness and paralysis, which cause respiratory arrest and ultimately result in death. Muscle twitching and fasciculations occur prior to depolarizing paralysis in severe OP poisoning. Because striated diaphragmatic and intercostal muscles paralyse, mechanical breathing is frequently required.

The intermediate syndrome, which appears after acute exposure to a few highly lipophilic OPs, is also concerning (Senanayake N & Karalliedde L 1987). The development of widespread weakness, which frequently results in respiratory failure required ventilatory support, characterises this illness, which appears a few days following a clearly characterised cholinergic phase (De Bleecker J et al., 1992). Its name refers to the fact that it often follows the initial cholinergic phase but comes before the delayed-neuropathic phase. A disease known as organophosphate induced delayed neuropathy (OPIDN) is caused by specific OPs inhibiting the esterase that is the focus of neuropathy. Weeks after an initial encounter, OPIDN usually starts to manifest. Paresthesias in the hands and feet are the first symptom, followed by sensory loss, weakness, ataxia, and flaccidity of the distal muscles. OPIDN sufferers may recover within a few months, but occasionally the consequences are long-lasting.

A few days after admission, ventricular dysrhythmias may be caused by myocardial damage caused directly by interstitial inflammation, myocarditis, or patchy pericarditis, as documented in post mortem histology (Kiss Z & Fazekas T

1983; Chacko J & Elangoyan A 2010; Anand S et al., 2009; Wang MH et al., 1998). At least three research (Chuang FR et al., 1996; Hrabetz H et al., 2013; Shadnia S et al., 2009) have discussed the predictive value of the QTc interval in relation to respiratory failure and mortality, however this is not a consistent conclusion (Akdur O et al., 2010; Yurumez Y et al., 2009). There are somewhat frequent reports of QT prolongation and Torsades de pointes (Wang MH et al., 1998; Bar-Meir E et al., 2007). There have been reports of pancreatitis and hyperamylasemia (Moore PG & James OF 1981) and one case study has a reported incidence of 12% of OP-poisoned patients (Sahin I et al., 2022). The most prevalent metabolic disorders are hyperglycemia and hypokalemia (Saadesh AM 2001).

Despite having identical animal toxicity, the human case fatality rate for acute self-poisoning with the organophosphorus (OP) pesticide dimethoate is three times higher than that of poisoning with chlorpyrifos. The typical clinical presentation of severe dimethoate poisoning differs significantly from that of chlorpyrifos and other OP pesticides in that many patients first exhibit hypotension, which then leads to shock and eventual death within 12-48 h of ingestion. This syndrome's pathogenesis is unclear.

Three patients with severe dimethoate toxicity shows clinically, all displayed extreme hypotension and inappropriate peripheral vasodilatation at presentation. This condition worsened in spite of therapy with atropine, intravenous fluids, pralidoxime chloride, and inotropes. All passed away 2.5 to 32 hours after admission. Little evidence for a primary cardiotoxic impact of dimethoate was revealed by continuous cardiac monitoring and troponin T measurement (Davies J et al., 2008). With dimethoate, this has proven a particular problem. Direct-acting vasopressors should be used to treat hypotension that is resistant to fluid resuscitation; the choice of agent depends on the patient's unique physiologic factors. Methylene blue or lipid emulsion therapy are a few of other treatments or drugs that can be used to treat refractory shock (Jang DH et al., 2013). Both of these treatments should be regarded as off-label uses because neither has been studied in the context of OP toxicity.

7. Management of OP poisoning

Based on clinical suspicion, the recognisable clinical symptoms (Table 3), and the smell of pesticides or solvents, OP poisoning is diagnosed. The best way to validate it would be with a test that measures BuChE activity in plasma (or AChE in whole blood) (Lotti M 2001). There are normally 2 techniques to certify exposure. The first technique involves looking for organophosphorus metabolites in the urine, such as para-nitrophenol or dialkyl phosphate. The second method, which involves measuring AChE, is most helpful when a diagnosis is difficult to make or when modest or persistent toxicity is apparent. For emergency clinicians, cholinesterase activity levels are frequently difficult to obtain within a useful time frame. (Rehiman S et al., 2008; Aygun D et al., 2002; Rajapakse BN et al., 2011). Laboratory testing, however, can give helpful guidelines to follow when caring for a patient who is drunk and can provide information on the course of the disease and the therapeutic response (Eddleston M et al., 2005; Coye MJ et al., 1987; Lifshitz M et al., 1999; Davies Jo et al., 2008; Yager J et al., 1976).

The chosen test to assess the efficacy of oxime is erythrocyte cholinesterase activity since it best correlates with neuronal AChE activity at the neuromuscular junction (Thiermann H et al., 2005). The use of plasma cholinesterase assays is impacted by a number of mitigating factors and variances, which can limit the usefulness of plasma cholinesterase activity. (Eddleston M et al., 2005; Coye MJ et al., 1987; Lifshitz M et al., 1999; Davies Jo et al., 2008; Yager J et al., 1976; Coye MJ et al., 1986).

Table 3
Clinical features of Organophosphate poisoning

Muscarinic receptor	Nicotinic receptor	Muscarinic & Nicotinic receptor in CNS	Nicotinic receptor at neuromuscular Junction
Bronchospasm	Tachycardia	Agitation	Fasciculation's
Bronchorhea	Hypertension	Respiratory failure	Muscle weakness
Meiosis	Mydriasis	Comatose	Paralysis
Lacrimation	Sweating	confusion	
Urination			
Diarrhea			
Hypotension			
Bradycardia			
Vomiting			
Salivation			

7.1 Clinical Management of OP poisoning

Before patients arrive at the healthcare facility, removal from the source and patient decontamination are frequently carried out. Ideally, this work should be done by healthcare professionals wearing the proper personal protective equipment. It is advised that level C personal protective equipment be worn by appropriately qualified, hospital-based healthcare professionals, even though secondary contamination from exposed individuals is probably limited (Macintyre AG et al., 2000). Only after first stabilisation and injury assessment should additional disinfection be considered. It may be possible to significantly limit residual exposure to the patient and prevent fume off-gassing by taking off all clothing and equipment (Kales SN, Christiani D 2004). After that, the patient should be cleaned off with soap and water. Military reactive skin decontamination lotion towelettes, sponges, and diluted alkaline soap are some alternate decontamination techniques (Sidell FR, Borak J 1992).

Most victims of OP exposure pass away through seizures or loss of airway and respiratory drive. Salivation, emesis, aspiration, bronchospasm, pulmonary edema, convulsions, CNS depression, muscle weakness, and overt paralysis are among conditions that can endanger the patency of the airways. Early airway and breathing control is frequently necessary in severely poisoned individuals, and decontamination may need to be done at the same time. Because oxygenation could not be possible until secretions are under control, rapid atropinization

should begin even before oxygen administration (Konickx LA et al., 2014; Eddleston M et al., 2004). Depending on the clinical condition and the patient's reaction to aggressive and early atropinization, rapid sequence intubation may be necessary. Rapid sequence intubation using succinylcholine will result in protracted paralysis since succinylcholine is degraded by plasma cholinesterases Sener EB et al., 2002; Selden BS & Curry SC 1987). Despite not being prohibited, succinylcholine is not recommended for rapid sequence intubation; instead, short-acting, non-depolarizing drugs are preferable. Aggressive seizure management with benzodiazepines is crucial because seizures with cholinesterase-inhibiting drug overdose can be fatal. This medication may also increase survival, protect the CNS, and prevent cardiac dysrhythmia (Koenig KL et al., 2008). Any parenteral benzodiazepine may be administered, but given its quick onset and simplicity of titration, an initial dose of 10 mg of intravenous diazepam is advised. However, any GABAergic drug is likely to be useful. Midazolam or lorazepam can be administered intramuscularly in the absence of quick intravenous access. It is unlikely that other frequently used anticonvulsants will work (Shih T et al., 1999).

However, emesis is prevalent, thus further removal via gastric aspiration or lavage is unlikely to have a significant benefit. Gastrointestinal cleaning following OP intake is of unknown efficacy. A mechanical decontamination attempt may result in pulmonary aspiration and pneumonitis since OPs are frequently dissolved in different hydrocarbons. However, if the patient's airway is secure or protected and the right circumstances are met, it would be ethical to attempt stomach aspiration. To avoid absorbing too much of the chemical, further decontamination with activated charcoal can be appropriate. However, a sizable prospective, randomized clinical trial for all cases of self-poisoning in rural Asia did not discover better outcomes when multidose activated charcoal was administered (Eddleston M et al., 2008).

8. Therapeutic Options for OP poisoning:

Atropine and oxygen delivery are thought to be the cornerstones of treatment after initial resuscitation to keep the airway, breathing, and circulation open. Although their efficacy is hotly contested, an AChE reactivator (an oxime that reactivates AChE by removing the phosphate group) is also employed (De Silva HJ et al., 1992; Singh S et al., 1995; Peter JV 2000). The patient's stabilisation and resuscitation should be treated as top priorities. If a considerable amount of pesticides have been consumed and symptoms appear within 1-2 hours of administration, gastric decontamination should only be considered after this (American Academy of Clinical Toxicology 1997). After stabilisation, patients must be closely monitored for changes in atropine requirements, deteriorating respiratory function caused by intermediate syndrome, and recurring cholinergic characteristics occurring with OP drugs that are fat soluble. The therapy of OP poisoning is provided below

An overview of the therapy of OP poisoning: (Clark, R. F. 2002; Eddleston M et al., 2004; Aaron CK In: Shannon et al., 2006)

- ❖ Examine breathing, circulation, and airways. To lessen the risk of aspirating stomach contents, arrange the patient in the left lateral position, preferably

with the head lower than the feet. If it's accessible, give high flow oxygen. If the patient's breathing or airway is damaged, intubate them.

- ❖ Based on the severity, establish intravenous (iv) infusion and provide a bolus of 1-3 mg atropine. Arrange a 0-9 percent normal saline infusion while attempting to maintain systolic blood pressure at 80 mm Hg and urine output over 0.5 mL/kg/h.
- ❖ When giving the initial atropine dose, take note of heart rate, blood pressure, pupil size, whether patient was sweating, and if any auscultation is present.
- ❖ By giving pralidoxime chloride 2 g (or obidoxime 250 mg) intravenously over 20-30 minutes into a second cannula, followed by an infusion of pralidoxime 0.5-1 g/h (or obidoxime 30 mg/hr) in 0-9% normal saline.
- ❖ Check their vitals such as pulse, blood pressure, pupil size, sweat, and chest sounds five minutes after giving the atropine to OP poisoned patient. Give double the initial dose of atropine if the condition has not improved.
- ❖ Every 5 minutes, keep reviewing of the patient; if no response occurs, use atropine in double dosages. Don't double the dose when the metrics start to get better. Similar or lower dosages may be employed.
- ❖ Atropine should be administered until the heart rate reaches 80 beats per minute, the systolic blood pressure reaches 80 mm Hg, and the chest is clear (understanding that atropine won't remove aspirational focal points). Most often, sweating stops. Since tachycardia can be brought on by a variety of circumstances, it is not a contraindication to atropine (Table 3). The pupils will frequently dilate, but because there will be late before the drug takes full effect, this indicator is not helpful for the first round of atropine therapy. Nevertheless, extremely dilated pupils are a sign of atropine poisoning.
- ❖ If the heart rate and blood pressure are just slightly below target however the chest is clear, clinical decisions is required regarding additional dosages of atropine. Maybe we don't need any more atropine right now. Vasopressors may be helpful in treating severe hypotension. It's not yet apparent how beneficial vasopressors are in comparison to taking more atropine (Buckley NA et al., 1994; Asari Y et al., 2004).
- ❖ After the patient has stabilised, begin an atropine infusion, providing every hour 10 to 20 percent of the total dose required to keep the patient stable. Ascertain frequently whether the patient is receiving the correct dosage of atropine. Cholinergic characteristics will eventually reappear if too little is provided (Eddleston M et al., 2004). Patients will become agitated and pyrexic, experience absent bowel noises, and experience urine retention if too much is given. If this occurs, stop the infusion and wait 30 to 60 minutes for these features to settle before starting the infusion again at a slower rate.
- ❖ Once atropine is not required for 12-24 hours, the patient is extubated and the oxime infusion is kept on.
- ❖ Review the respiratory system operation again. Patients should be intubated and ventilated if their vital capacity is less than 15 mL/kg, their tidal volume is less than 5 mL/kg, they experience apnoeic spells, or their PaO₂ is less than 8 kPa (60 mm Hg) on a FIO₂ of greater than 60%.
- ❖ Patients who are conscious are often asked to lift their heads off the bed and maintain that position while having pressure put on their foreheads to

measure their flexor neck strength. Any indication of a patient's vulnerability to developing peripheral respiratory failure is weakness (intermediate syndrome). In such patients, tidal volume should be assessed every 4 hours. Values below 5 mL/kg show that intubation and ventilation are necessary.

- ❖ Atropine dosage should be reviewed to treat agitation, and benzodiazepines should be used appropriately to sedate the patient. Atropine dramatically increases the risk of severe hyperthermia when agitated patients are physically restrained in warm environments because it suppresses typical thermoregulatory responses, such as sweating. Therefore, it's crucial to get enough sedative.
- ❖ Keep a close eye out for recurrent cholinergic crises brought on by the release of fat-soluble organophosphorus from fat reserves. Even days or weeks after ingesting some organophosphorus, such crises can still happen. Patients with recurrent cholinergic symptoms will require atropine and oxime retreatment.

9. Dose and Administration of current drugs for OP poisoning

9.1 Atropine

For the treatment of acute OP poisoning, atropine continues to be the cornerstone of care, however, now some encouraging treatments are being developed. It counteracts the parasympathetic effects of excess acetylcholine at the peripheral and central muscarinic receptors by acting competitively at these locations. Rapid continuous intravenous infusion of enough atropine should be administered to stabilise the patient. Atropine dosage recommendations have not been established (Eddleston et al., 2004) It differs amongst poisoned patients due of variations in the dose and specific OP chemical consumed, as well as probably because an oxime was also administered (oximes have been suggested to have anticholinergic activity at large doses) (John MK et al., 2000). It is important to keep in mind that utilising atropine at doses lower than 0.6 mg could paradoxically make the condition worse by causing bradycardia due to the activation of M1 auto receptors, which are more sensitive to acetylcholine than M2 receptors (Wellstein A & Pitschner HF 1998).

By assessing the improvement in cardiovascular function (systolic blood pressure >80 mmHg, pulse rate >80 bpm), as well as respiratory function, the treatment is provided in accordance with the aforementioned recommendations, with doses being doubled every 5 minutes (no bronchorrhea and bronchospasm). The method will allow for the gradual administration of up to 70 mg of atropine to a patient in less than 30 minutes, leading to quick stabilization and a reduced risk of atropine poisoning. An intravenous infusion is started to maintain the therapeutic benefits of atropine once the patient meets the majority of the atropine therapy's desired endpoints, i.e., is completely atropinized. While there are several ways to administer atropine intravenously, the recommendations call for an infusion to be given every hour at a rate of 20% of the total dose required to stabilize the patient at first, to continue for the first 48 hours, and then to gradually reduce the dose over the following hours and days.

A dose of atropine that is too high might cause delirium, agitation, heat, absence of bowel sounds, and urine retention, among other side effects (Heath AJW & Meredith T 1992). If this occurs, cease the infusion and wait for these features to stabilise for 30 to 60 minutes before restarting at 70 to 80 percent of the prior infusion rate.

9.2 Oximes

AChE that has been blocked by OP poisoning is reactivated by oximes (such as pralidoxime, obidoxime, and HI-6). Ageing of the AChE and excessive pesticide concentrations hinder reactivation. Diethyl OP compounds age AChE more slowly than dimethyl OP compounds. Theoretically, for diethyl OP poisoning, oximes may be effective if administered within 120 hours, and for dimethyl OP poisoning, within 12 hours. As long as the patient exhibits symptoms, treatment may be useful since it may take several days for the pesticide concentration to fall below the level at which the rate of reactivation exceeds the rate of re-inhibition (Eyer P 2003).

The therapeutic effectiveness of oximes is currently supported by conflicting data, and some OP pesticides do not react favorably to oximes. It is difficult to disagree with the World Health Organization (WHO) recommendations to administer high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8-10 mg/kg/hour for the first two days) to everyone who has OP poisoning, particularly in individuals who exhibit nicotinic symptoms (International programme on chemical safety Geneva 1999). Oximes can cause hypertension, cardiac dysrhythmias, epigastric pain, headache, blurred vision, disorientation, and cardiac arrest after rapid delivery. Only when pralidoxime is administered quickly or in doses > 30 mg/kg bolus have adverse effects with this medication been recorded. It could be challenging to tell these negative consequences from organophosphorus effects (Bismuth C et al., 1992). If there is clinical deterioration with oxime withdrawal, the infusion can be reduced after two days and reintroduced. However, a recent study found that the outcomes of patients with OP poisoning were improved when PAM dosages were determined by the severity of the patient rather than by rigidly adhering to WHO recommendations (Lin CC et al., 2016).

9.3 Use of Benzodiazepines in organophosphate poisoning

The first-line treatment for agitation and seizures in an emergency is a medicine called a benzodiazepine (Trinka E 3rd ed. 2009). They bind to GABA-A receptors, increasing the frequency at which channels open at the receptor. This results in an increase in chloride conductance and neuronal hyperpolarization, which enhances inhibitory neurotransmission and has antiepileptic effects (Trinka E et al., 2015). Diazepam has been shown in animal experiments to both prevent and treat the convulsions that OPs generate, as well as to potentially avoid the late effects of the central nervous system damage these convulsions cause. As a result, diazepam is a crucial component of the treatment plan for severe OP poisoning since it stops convulsions altogether or at least shortens their duration. Furthermore, based on case studies, diazepam may help lessen muscle

fasciculation, a subjectively painful symptom of OP pesticide exposure (Timothy C Marrs 2003).

10. Summary

Victims of OP poisoning experience a variety of effects. The severity of the poisoning (amount, duration, and agent), certain individual factors, such as one's intrinsic ability to metabolise certain OPs, preexisting disease, the length of time it takes to start receiving medical treatment, access to specialists, and hospital capabilities all affect how the patient will fare. Mortality rates are still high despite adequate supportive and antidotal care, particularly in cases of OP poisoning. Antimuscarinic drugs and oximes are aggressively and early administered as part of therapy. Following the resolution of acute cholinergic toxicity, patients who have ingested OPs should be continuously monitored for the emergence of the intermediate syndrome and Organophosphate delayed induced neuropathy (OPIDN).

Conflict of Interest: Authors declare no conflict of Interest.

Acknowledgement

The authors are grateful to the Indian Council of Medical Research (ICMR) and the Director of the National Institute of Nutrition (ICMR-NIN), Hyderabad, for encouragement and support.

Reference

- Aaron, C. K. (2007). Organophosphates and carbamates. In Haddad and Winchester's clinical management of poisoning and drug overdose (pp. 1171-1184). WB Saunders.
- Abhilash, P. C., & Singh, N. (2009). Pesticide use and application: an Indian scenario. *Journal of hazardous materials*, 165(1-3), 1-12.
- Akdur, O., Durukan, P., Ozkan, S., Avsarogullari, L., Vardar, A., Kavalci, C., & Ikizceli, I. (2010). Poisoning severity score, Glasgow coma scale, corrected QT interval in acute organophosphate poisoning. *Human & experimental toxicology*, 29(5), 419-425.
- Alavanja, M. C., Sprince, N. L., Oliver, E., Whitten, P., Lynch, C. F., Gillette, P. P., ... & Zwerling, C. (2001). Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study. *American journal of industrial medicine*, 39(6), 557-563.
- Ambali, S. F., & Ayo, J. O. (2011). Sensorimotor performance deficits induced by chronic chlorpyrifos exposure in Wistar rats: mitigative effect of vitamin C. *Toxicological & environmental chemistry*, 93(6), 1212-1226.
- Position statement: gastric lavage. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *Journal of toxicology. Clinical toxicology*, 35(7), 711-719.
- Anand, S., Singh, S., Nahar Saikia, U., Bhalla, A., Paul Sharma, Y., & Singh, D. (2009). Cardiac abnormalities in acute organophosphate poisoning. *Clinical Toxicology*, 47(3), 230-235.

- Asari, Y., Kamijyo, Y., & Soma, K. (2004). Changes in the hemodynamic state of patients with acute lethal organophosphate poisoning. *Veterinary and human toxicology*, *46*(1), 5-9.
- Ather, N. A., Ara, J. A. M. A. L., Khan, E. A., Sattar, R. A., & Durrani, R. A. S. H. I. D. (2008). Acute organophosphate insecticide poisoning. *J Surg Pak*, *13*(2), 71-4.
- Aygun, D., Doganay, Z., Altintop, L., Guven, H., Onar, M., Deniz, T., & Sunter, T. (2002). Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. *Journal of toxicology: clinical toxicology*, *40*(7), 903-910.
- Balali-Mood, M., & Shariat, M. (1998). Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *Journal of Physiology-Paris*, *92*(5-6), 375-378.
- Bar-Meir, E., Schein, O., Eisenkraft, A., Rubinshtein, R., Grubstein, A., Militianu, A., & Glikson, M. (2007). Guidelines for treating cardiac manifestations of organophosphates poisoning with special emphasis on long QT and Torsades De Pointes. *Critical reviews in toxicology*, *37*(3), 279-285.
- Bird, S. B., Gaspari, R. J., & Dickson, E. W. (2003). Early death due to severe organophosphate poisoning is a centrally mediated process. *Academic Emergency Medicine*, *10*(4), 295-298.
- Bismuth, C., Inns, R. H., & Marrs, T. C. (1992). Efficacy, toxicity and clinical use of oximes in anticholinesterase poisoning. *BUTTERWORTH-HEINEMANN, STONEHAM, MA(USA)*. 1992.
- Blackburn, G. M. (1981). Phosphonates as analogues of biological phosphates. *7*, 134-138.
- Bradberry, S. M., & Vale, J. A. (2005). Organophosphorus and carbamate insecticides. Brent J, Wallece K, Burkhart K, Phillips S, Donovan JW. *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient. Philadelphia: Mosby*, 937-46.
- Buckley, N. A., Dawson, A. H., & Whyte, I. M. (1994). Organophosphate poisoning: peripheral vascular resistance—a measure of adequate atropinization. *Journal of Toxicology: Clinical Toxicology*, *32*(1), 61-68.
- Calvert, G. M., Plate, D. K., Das, R., Rosales, R., Shafey, O., Thomsen, C., ... & Lackovic, M. (2004). Acute occupational pesticide-related illness in the US, 1998–1999: surveillance findings from the SENSOR-pesticides program. *American journal of industrial medicine*, *45*(1), 14-23.
- Chacko, J., & Elangovan, A. (2010). Late onset, prolonged asystole following organophosphate poisoning: a case report. *Journal of Medical Toxicology*, *6*(3), 311-314.
- Chuang, F. R., Jang, S. W., Lin, J. L., Chern, M. S., Chen, J. B., & Hsu, K. T. (1996). QTc prolongation indicates a poor prognosis in patients with organophosphate poisoning. *The American journal of emergency medicine*, *14*(5), 451-453.
- Clark, R. F. (2002). Insecticides: organic phosphorus compounds and carbamates. *Goldfrank's toxicologic emergencies*, *8*, 1497-512.
- Coye, M. J., Barnett, P. G., Midtling, J. E., Velasco, A. R., Romero, P., Clements, C. L., ... & Lowry, L. (1986). Clinical confirmation of organophosphate poisoning of agricultural workers. *American journal of industrial medicine*, *10*(4), 399-409.
- Coye, M. J., Barnett, P. G., Midtling, J. E., Velasco, A. R., Romero, P., Clements, C. L., & Rose, T. G. (1987). Clinical confirmation of organophosphate poisoning

- by serial cholinesterase analyses. *Archives of internal medicine*, 147(3), 438-442.
- Davies, J. O., Eddleston, M., & Buckley, N. A. (2008). Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. *QJM: An International Journal of Medicine*, 101(5), 371-379.
- Davies, J., Roberts, D., Eyer, P., Buckley, N., & Eddleston, M. (2008). Hypotension in severe dimethoate self-poisoning. *Clinical toxicology*, 46(9), 880-884.
- De Bleecker, J., Van Den Neucker, K., & Willems, J. (1992). The intermediate syndrome in organophosphate poisoning: presentation of a case and review of the literature. *Journal of Toxicology: Clinical Toxicology*, 30(3), 321-329.
- Dekundy, A., Kaminski, R. M., Zielinska, E., & Turski, W. A. (2007). NMDA antagonists exert distinct effects in experimental organophosphate or carbamate poisoning in mice. *Toxicology and applied pharmacology*, 219(2-3), 114-121.
- De Silva, H. J., Wijewickrema, R., & Senanayake, N. (1992). Does pralidoxime affect outcome of management in acute organophosphorus poisoning?. *The Lancet*, 339(8802), 1136-1138.
- Dickson, E. W., Bird, S. B., Gaspari, R. J., Boyer, E. W., & Ferris, C. F. (2003). Diazepam inhibits organophosphate-induced central respiratory depression. *Academic emergency medicine*, 10(12), 1303-1306.
- Eddleston, M., Buckley, N. A., Checketts, H., Senarathna, L., Mohamed, F., Sheriff, M. R., & Dawson, A. (2004). Speed of initial atropinisation in significant organophosphorus pesticide poisoning—a systematic comparison of recommended regimens. *Journal of Toxicology: Clinical Toxicology*, 42(6), 865-875.
- Eddleston, M., Dawson, A., Karalliedde, L., Dissanayake, W., Hittarage, A., Azher, S., & Buckley, N. A. (2004). Early management after self-poisoning with an organophosphorus or carbamate pesticide—a treatment protocol for junior doctors. *Critical Care*, 8(6), 1-7.
- Eddleston, M., Eyer, P., Worek, F., Mohamed, F., Senarathna, L., von Meyer, L., ... & Buckley, N. A. (2005). Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. *The Lancet*, 366(9495), 1452-1459.
- Eddleston, M., Juszczak, E., Buckley, N. A., Senarathna, L., Mohamed, F., Dissanayake, W., ... & Ox-Col Poisoning Study collaborators. (2008). Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *The Lancet*, 371(9612), 579-587.
- Eddleston, M., Karalliedde, L., Buckley, N., Fernando, R., Hutchinson, G., Isbister, G., ... & Smit, L. (2002). Pesticide poisoning in the developing world—a minimum pesticides list. *The Lancet*, 360(9340), 1163-1167.
- Eddleston, M. (2018). Insecticides: organic phosphorus compounds and carbamates. *Goldfrank's Toxicologic Emergencies*, ed. LS Nelson, MA Howland, NA Lewin, SW Smith, LR Goldfrank, RS Hoffman, pp. 1486-1502. New York: McGraw-Hill Education/Medical. 11th ed.
- Eyer, P. (2003). The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicological reviews*, 22(3), 165-190.
- Gunnell, D., Eddleston, M., Phillips, M. R., & Konradsen, F. (2007). The global distribution of fatal pesticide self-poisoning: systematic review. *BMC public health*, 7(1), 1-15.

- Henretig, F. M., Kirk, M. A., & McKay Jr, C. A. (2019). Hazardous chemical emergencies and poisonings. *New England journal of medicine*, 380(17), 1638-1655.
- Heath, A. J. W. (1992). Atropine in the management of anticholinesterase poisoning. *Clinical and Experimental Toxicology of Organophosphates and Carbamates.*, 543-554.
- Hrabetz, H., Thiermann, H., Felgenhauer, N., Zilker, T., Haller, B., Nährig, J., ... & Eyer, F. (2013). Organophosphate poisoning in the developed world—a single centre experience from here to the millennium. *Chemico-biological interactions*, 206(3), 561-568.
- IPCS. (1998). Organophosphorus Pesticides. *International Programme on Chemical Safety Poisons Information Monograph G001. updated 1999.* [Cited 2016 July 8]. Available from: <http://www.inchem.org/documents/pims/chemical/pimg001.htm>
- Jang, D. H., Nelson, L. S., & Hoffman, R. S. (2013). Methylene blue for distributive shock: a potential new use of an old antidote. *Journal of Medical Toxicology*, 9(3), 242-249.
- Johnson, M. K., Jacobsen, D., Meredith, T. J., Eyer, P., Heath, A. J., Ligtenstein, D. A., ... & Haines, J. A. (2000). Evaluation of antidotes for poisoning by organophosphorus pesticides. *Emergency Medicine*, 12(1), 22-37.
- Mrcp, J. J., Joubert, P. H., van der Spuy, M., & van Graan, E. (1984). Acute organophosphate poisoning presenting with choreo-athetosis. *Journal of Toxicology: Clinical Toxicology*, 22(2), 187-191.
- Kales, S. N., & Christiani, D. C. (2004). Acute chemical emergencies. *New England Journal of Medicine*, 350(8), 800-808.
- Karunarathne, A., Gunnell, D., Konradsen, F., & Eddleston, M. (2020). How many premature deaths from pesticide suicide have occurred since the agricultural Green Revolution?. *Clinical toxicology*, 58(4), 227-232.
- Katzung, B. G. (2004). Section II: Autonomic drugs. introduction to autonomic pharmacology. *Basic and Clinical Pharmacology*. New York: McGraw-Hill, 75-93.
- Kazemi, M., Tahmasbi, A. M., Valizadeh, R., Naserian, A. A., & Soni, A. (2012). Organophosphate pesticides: A general review. *Agricultural science research journals*, 2.
- King, A. M., & Aaron, C. K. (2015). Organophosphate and carbamate poisoning. *Emergency Medicine Clinics*, 33(1), 133-151.
- Kır, M. Z., Öztürk, G., Gürler, M., Karaarslan, B., Erden, G., Karapirli, M., & Akyol, Ö. (2013). Pesticide poisoning cases in Ankara and nearby cities in Turkey: an 11-year retrospective analysis. *Journal of forensic and legal medicine*, 20(4), 274-277.
- Kiss, Z., & Fazekas, T. (1983). Organophosphates and torsade de pointes ventricular tachycardia. *Journal of the royal society of medicine*, 76(11), 984-985.
- Kishi, M., & LaDou, J. (2001). Introduction: international pesticide use. *International Journal of Occupational and Environmental Health*, 7(3), 259-265.
- Koelle, G. B. (1992). Pharmacology and Toxicology of organophosphates and carbonates. In: *Clinical and experimental toxicology of organophosphates and carbonates.*

- Koenig, K. L., Boatright, C. J., Hancock, J. A., Denny, F. J., Teeter, D. S., Kahn, C. A., & Schultz, C. H. (2008). Health care facility-based decontamination of victims exposed to chemical, biological, and radiological materials. *The American journal of emergency medicine*, *26*(1), 71-80.
- Konickx, L. A., Bingham, K., & Eddleston, M. (2014). Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning?—A cohort study. *Clinical Toxicology*, *52*(5), 531-537.
- Kozhemyakin, M., Rajasekaran, K., & Kapur, J. (2010). Central cholinesterase inhibition enhances glutamatergic synaptic transmission. *Journal of neurophysiology*, *103*(4), 1748-1757.
- Kumar, S. V., Fareedullah, M. D., Sudhakar, Y., Venkateswarlu, B., & Kumar, E. A. (2010). Current review on organophosphorus poisoning. *Archives of applied science research*, *2*(4), 199-215.
- Lifshitz, M., Shahak, E., & Sofer, S. H. A. U. L. (1999). Carbamate and organophosphate poisoning in young children. *Pediatric emergency care*, *15*(2), 102-103.
- Lin, C. C., Hung, D. Z., Chen, H. Y., & Hsu, K. H. (2016). The effectiveness of patient-tailored treatment for acute organophosphate poisoning. *biomedical journal*, *39*(6), 391-399.
- Litchfield, M. H. (2005). Estimates of acute pesticide poisoning in agricultural workers in less developed countries. *Toxicological reviews*, *24*(4), 271-278.
- Lotti, M. (2001). Clinical toxicology of anticholinesterase agents in humans. *Handbook of Pesticide Toxicology. Academic Press, USA, Ed. II, 2*, 1043.
- Macintyre, A. G., Christopher, G. W., Eitzen Jr, E., Gum, R., Weir, S., DeAtley, C., ... & Barbera, J. A. (2000). Weapons of mass destruction events with contaminated casualties: effective planning for health care facilities. *Jama*, *283*(2), 242-249.
- Mancini, F., Van Bruggen, A. H., Jiggins, J. L., Ambatipudi, A. C., & Murphy, H. (2005). Acute pesticide poisoning among female and male cotton growers in India. *International journal of occupational and environmental health*, *11*(3), 221-232.
- Mathur, S. C., & Tannan, S. K. (1999). Future of Indian pesticides industry in next millennium. *Pesticide information*, *24*(4), 9-23.
- Mathur, H. B., Johnson, S., & Kumar, A. (2003). Analysis of pesticide residues in soft drinks. *Centre for Science and Environment, New Delhi, India*.
- Moore, P. G., & James, O. F. (1981). Acute pancreatitis induced by acute organophosphate poisoning?. *Postgraduate medical journal*, *57*(672), 660-662.
- Mostafalou, S., & Abdollahi, M. (2013). Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicology and applied pharmacology*, *268*(2), 157-177.
- Murali, R., Bhalla, A., Singh, D., & Singh, S. (2009). Acute pesticide poisoning: 15 years experience of a large North-West Indian hospital. *Clinical toxicology*, *47*(1), 35-38.
- Murray, D., Wesseling, C., Keifer, M., Corriols, M., & Henao, S. (2002). Surveillance of pesticide-related illness in the developing world: putting the data to work. *International journal of occupational and environmental health*, *8*(3), 243-248.
- Namba, T., Nolte, C. T., Jackrel, J., & Grob, D. (1971). Poisoning due to organophosphate insecticides: acute and chronic manifestations. *The American journal of medicine*, *50*(4), 475-492.

- Oliveira-Silva, J. J., Alves, S. R., Meyer, A., Perez, F., Sarcinelli, P. D. N., Mattos, R. D. C. O., & Moreira, J. C. (2001). Influence of social-economic factors on the pesticide poisoning, Brazil. *Revista de Saúde Pública*, 35, 130-135.
- Pereira, E. F., Aracava, Y., DeTolla, L. J., Beecham, E. J., Basinger, G. W., Wakayama, E. J., & Albuquerque, E. X. (2014). Animal models that best reproduce the clinical manifestations of human intoxication with organophosphorus compounds. *Journal of Pharmacology and Experimental Therapeutics*, 350(2), 313-321.
- Peshin, S. S., Srivastava, A., Halder, N., & Gupta, Y. K. (2014). Pesticide poisoning trend analysis of 13 years: a retrospective study based on telephone calls at the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. *Journal of forensic and legal medicine*, 22, 57-61.
- Peter, J. V., & Cherian, A. M. (2000). Organic insecticides. *Anaesthesia and intensive care*, 28(1), 11-21.
- Peter, J. V., Sudarsan, T. I., & Moran, J. L. (2014). Clinical features of organophosphate poisoning: A review of different classification systems and approaches. Indian journal of critical care medicine: peer-reviewed, official publication of *Indian Society of Critical Care Medicine*, 18(11), 735.
- Maiti, P. P., Dubey, S., & Saha, P. (2011). Study of various poisoning: a review. *Indo Global J Pharmaceut Sci*, 1(4), 304-314.
- Rajapakse, B. N., Thiermann, H., Eyer, P., Worek, F., Bowe, S. J., Dawson, A. H., & Buckley, N. A. (2011). Evaluation of the Test-mate ChE (cholinesterase) field kit in acute organophosphorus poisoning. *Annals of emergency medicine*, 58(6), 559-564.
- Rehiman, S., Lohani, S. P., & Bhattarai, M. C. (2008). Correlation of serum cholinesterase level, clinical score at presentation and severity of organophosphorous poisoning. *J Nepal Med Assoc*, 47(170), 47-52.
- Saadeh, A. M. (2001). Metabolic complications of organophosphate and carbamate poisoning. *Tropical doctor*, 31(3), 149-152.
- Sahin, I. C., Onbasi, K., Sahin, H., Karakaya, C. E. N. G. İ. Z., Ustun, Y. U. S. U. F., & Noyan, T. E. V. F. İ. K. (2002). The prevalence of pancreatitis in organophosphate poisonings. *Human & experimental toxicology*, 21(4), 175-177.
- Sakamoto, T., Sawada, Y., Nishide, K., Sadamitsu, D., Yoshioka, T., Sugimoto, T., ... & Kishi, H. (1984). Delayed neurotoxicity produced by an organophosphorous compound (Sumithion). A case report. *Archives of toxicology*, 56(2), 136-138.
- Selden, B. S., & Curry, S. C. (1987). Prolonged succinylcholine-induced paralysis in organophosphate insecticide poisoning. *Annals of emergency medicine*, 16(2), 215-217.
- Senanayake, N., & Peiris, H. (1995). Mortality due to poisoning in a developing agricultural country: trends over 20 years. *Human & experimental toxicology*, 14(10), 808-811.
- Senanayake, N., & Sanmuganathan, P. S. (1995). Extrapyramidal manifestations complicating organophosphorus insecticide poisoning. *Human & experimental toxicology*, 14(7), 600-604.
- Senarathna, L., Jayamanna, S. F., Kelly, P. J., Buckley, N. A., Dibley, M. J., & Dawson, A. H. (2012). Changing epidemiologic patterns of deliberate self poisoning in a rural district of Sri Lanka. *BMC public health*, 12(1), 1-8.
- Senanayake, N., & Karalliedde, L. (1987). Neurotoxic effects of organohosphorus insecticides. *New England Journal of Medicine*, 316(13), 761-763.

- Sener, E. B., Ustun, E., & Kocamanoglu, S. (2002). Prolonged succinylcholine-induced paralysis in OP insecticide poisoning. *Acta Anaesthesiol Scand*, *46*(8), 1046-8.
- Shadnia, S., Okazi, A., Akhlaghi, N., Sasanian, G., & Abdollahi, M. (2009). Prognostic value of long QT interval in acute and severe organophosphate poisoning. *Journal of medical toxicology*, *5*(4), 196-199.
- Shahar, E., & Andraws, J. (2001). Extra-pyramidal parkinsonism complicating organophosphate insecticide poisoning. *European Journal of Paediatric Neurology*, *5*(6), 261-264.
- Shih, T. M., McDonough Jr, J. H., & Koplovitz, I. (1999). Anticonvulsants for Soman-induced seizure activity. *Journal of biomedical science*, *6*(2), 86-96.
- Sidell, F. R., & Borak, J. (1992). Chemical warfare agents: II. Nerve agents. *Annals of emergency medicine*, *21*(7), 865-871.
- Singh, S., Batra, Y. K., Singh, S. M., Wig, N., & Sharma, B. K. (1995). Is atropine alone sufficient in acute severe organophosphorus poisoning?: experience of a North West Indian Hospital. *International journal of clinical pharmacology and therapeutics*, *33*(11), 628-630.
- Singh, S., Sharma, B. K., Wah, P. L., Anand, B. S., & Chugh, K. S. (1984). Spectrum of acute poisoning in adults (10 year experience). *The Journal of the Association of Physicians of India*, *32*(7), 561-563.
- Taylor P (1996). Anticholinesterase agents. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. Ed. by Hardman J.G., Limbird L.E., Molinoff P.B. and Ruddon R.W. 9th ed. 1996. P. 161-76
- Thiermann, H., Szinicz, L., Eyer, P., Zilker, T., & Worek, F. (2005). Correlation between red blood cell acetylcholinesterase activity and neuromuscular transmission in organophosphate poisoning. *Chemico-biological interactions*, *157*, 345-347.
- Thomas, M., Anandan, S., Kuruville, P. J., Singh, P. R., & David, S. (2000). Profile of hospital admissions following acute poisoning--experiences from a major teaching hospital in south India. *Adverse drug reactions and toxicological reviews*, *19*(4), 313-317.
- Thundiyil, J. G., Stober, J., Besbelli, N., & Pronczuk, J. (2008). Acute pesticide poisoning: a proposed classification tool. *Bulletin of the World Health Organization*, *86*, 205-209.
- Marrs, T. C. (2003). Diazepam in the treatment of organophosphorus ester pesticide poisoning. *Toxicological reviews*, *22*(2), 75-81.
- Tinoco-Ojanguren, R., & Halperin, D. C. (1998). Poverty, production, and health: inhibition of erythrocyte cholinesterase via occupational exposure to organophosphate insecticides in Chiapas, Mexico. *Archives of Environmental Health: An International Journal*, *53*(1), 29-35.
- Trinka, E. (2009). Benzodiazepines used primarily for emergency treatment (diazepam, lorazepam, and midazolam) In: Shorvon SD, Perucca E, Engel J Jr, editors. Treatment of epilepsies. 3.
- Trinka, E., Höfler, J., Leitinger, M., & Brigo, F. (2015). Pharmacotherapy for status epilepticus. *Drugs*, *75*(13), 1499-1521.
- Walter FG editor. (3rd edition). (2003). Advanced Hazmat life support provider manual. Arizona Board of reagents for the university of AZ, Tucson.
- Wanner, B. L., & Metcalf, W. W. (1992). Molecular genetic studies of a 10.9-kb operon in *Escherichia coli* for phosphonate uptake and biodegradation. *FEMS microbiology letters*, *100*(1-3), 133-139.

- Wang, M. H., Tseng, C. D., & Bair, S. Y. (1998). QT interval prolongation and pleomorphic ventricular tachyarrhythmia (Torsade de pointes) in organophosphate poisoning: report of a case. *Human & experimental toxicology*, *17*(10), 587-590.
- Wellstein, A., & Pitschner, H. F. (1988). Complex dose-response curves of atropine in man explained by different functions of M1-and M2-cholinoceptors. *Naunyn-Schmiedeberg's archives of pharmacology*, *338*(1), 19-27.
- World Health Organization. (2020). Guidelines for establishing a poison centre.
- Yager, J., McLean, H., Hudes, M., & Spear, R. C. (1976). Components of variability in blood cholinesterase assay results. *Journal of Occupational Medicine*, *18*(4), 242-244.
- Yurumez, Y., Yavuz, Y., Saglam, H., Durukan, P., Ozkan, S., Akdur, O., & Yucel, M. (2009). Electrocardiographic findings of acute organophosphate poisoning. *The Journal of emergency medicine*, *36*(1), 39-42.
- Zhang, J., Stewart, R., Phillips, M., Shi, Q., & Prince, M. (2009). Pesticide exposure and suicidal ideation in rural communities in Zhejiang province, China. *Bulletin of the World Health Organization*, *87*(10), 745-753.
- Zwiener, R. J., & Ginsburg, C. M. (1988). Organophosphate and carbamate poisoning in infants and children. *Pediatrics*, *81*(1), 121-126.