Review Article

Organophosphate Poisoning: Review of Prognosis and Management

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Abstract

The high annual mortality rate of organophosphorus (OP) poisoning indicates that the treatment is mostly ineffective in this regard. It has been suggested to add calcium channel blocking (CCB) drugs or magnesium sulfate ($MgSO_4$) to normal care to decrease the release of acetylcholine (ACh) at the cholinergic synapse. Moreover, the diagnosis of OP poisoning is chiefly based on clinical evidence. Oximes and atropine are the recognized antidotes of OP. However, low-priced medications such as $MgSO_4$ and sodium bicarbonate ($NaHCO_3$), as well as novel adjunct therapies, have been introduced recently. Furthermore, antioxidants are recommended for managing OP poisoning. In addition, hemoperfusion, fresh frozen plasma (FFP), and K-oximes are a number of innovative management modalities that deserve further evaluation. However, prevention seems to be the most effective management modality in this respect. Therefore, this study aimed to briefly discuss the controversies in OP poisoning management and present recent advances in its management and prognosis. The results of this study revealed that multiple factors including type of exposure, acetylcholinesterase (AChE) plasma level, time of hospitalization, and severity confirming OP poisoning should be considered to provide the best treatment strategy.

Keywords: Atropine, Calcium channel blocking drug, Diagnosis, Fresh frozen plasma, hemoperfusion, magnesium sulfate, Management, Organophosphate, Poisoning, Oxime, Prognosis, Serum albumin, Sodium bicarbonate

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Submitted: 18-Nov-2022; **Revised:** 27-Jan-2024; **Accepted:** 11-Mar-2024; **Published:** 23-Sep-2024

Introduction

Organophosphate (OP) chemicals such as nerve gases such as soman and pesticides including parathion can be considered main chemical threat agents. The cholinergic crisis is in relation to exposure to acute OP. Neurobehavioral deficits such as mood changes, memory impairment, acquired epilepsy, and depression have been reported by OP toxicity survivors. According to recent reports, about 3 million OP poisonings have been recorded every year, of which at least 250,000 people have died.[1-3] According to reports from the United States, among the young population, one of the most common methods of suicide is self-poisoning. This is while the percentage of suicide using poison such as OP is reported to be higher in developing countries. According to the A2019 World Health Organization (WHO) report, the age of suicide has decreased.[2,4,5]

The mentioned points highlight the necessity of offering beneficial countermeasures to reduce the overwhelming outcomes in this respect. Exposure to acute OP is related to the spread of immediate symptoms named "cholinergic crises," which are normally recognized by increased secretions, followed by bradycardia, seizure and respiratory depression, and death.[6] The mentioned symptoms are the result of the

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_393_22

How to cite this article: Zoofaghari S, Maghami-Mehr A, Abdolrazaghnejad A. Organophosphate poisoning: Review of prognosis and management. Adv Biomed Res 2024;13:82.

effect of OP on the enzyme acetylcholinesterase (AChE) that instantly rises the synaptic availability of the neurotransmitter acetylcholine (ACh) and leads to the symptom presentation of cholinergic crises. Diisopropyl fluorophosphate (DFP), paraoxon (POX), and other OP chemicals are powerful enzyme AChE inhibitors,[7] which can hinder the breakdown of the neurotransmitter ACh. The classical cholinergic crisis is caused by the overstimulation of ACh receptors. This crisis is recognized by lacrimation, salivation, defecation, and urination that are subsequently followed by bradycardia and respiratory depression. Moreover, tonic-clonic seizures, status epilepticus (SE), muscle fasciculation, and prolonged seizure activity are caused by nicotinic receptor stimulation and can cause death in case of being left untreated.[8] Following the release of excitatory neurotransmitter glutamate downstream of acetyl hyperstimulation, SE activity appears to involve the recruitment of N-methyl-d-aspartate (NMDA) receptors.[9-11]

Carbamate and OP compounds hinder AChE and other esterases and result in increased ACh concentration and overstimulation in cholinergic synapses in the central nervous system, neuromuscular junction (NMJ), and autonomic nervous system. The chief cause of death during an acute cholinergic crisis is acute respiratory failure that is caused by NMJ dysfunction, bronchorrhea, and reduced central respiratory drive.[12,13] Moreover, delayed NMJ dysfunction might take place following the acute cholinergic syndrome development in OP insecticide poisoning (moderate syndrome or type II respiratory failure), which would prolong the necessity of ventilation and expose the patients to pneumonia and other ventilation complications. The development of delayed polyneuropathy and OP-induced peripheral neuropathy (OPIDN) has been reported in a minor group of OP-poisoned patients a few weeks after the exposure.[14,15]

Treatment of acute severe anticholinesterase insecticide poisoning is tough as a novel therapy has not been presented in routine clinical practice over the last 50 years. Although antimuscarinic drug atropine is used for treating bronchorrhea and other muscarinic features of poisoning,[11,12] no specific therapy has been employed for treating central respiratory failure or acute NMJ dysfunction that requires treatment with mechanical ventilation. Despite effective atropine therapy,[12] the mortality rate of 10% in patients who survive till hospital admission has been reported. A number of oximes such as pralidoxime are employed for reactivating AChE following OP insecticide poisoning and possibly reducing the concentration of ACh at all cholinergic synapses; however, clear-cut evidence is not available at present.[16] Small-scale clinical trials have tested some potential therapies such as clonidine,[14] $MgSO_4$, and bicarbonate.[13] Magnesium that is identical to calcium channel blocking (CCB) drugs such as nimodipine works by blocking calcium channels and results in the reduction of ACh release. Atropine, pralidoxime, and benzodiazepine including diazepam or midazolam are used in contemporary remedy strategies to manipulate the cholinergic disaster, reactivate pain, and control seizures, respectively.[15,17]

Moreover, contemporary antidotes are significant in restricting instantaneous mortality caused by OP exposure. OP poisoning survivors do not account for on-time mortality over a 2-week length following the initial survival and development of neurological morbidities comprising depression, cognitive deficits, and recurrent seizures.[18-21] This study addressed the controversial issues with respect to OP poisoning management and presented current advances in its management and prognosis.

Mechanism of Action of OP Poisoning

OP compounds include phosphorous acid and carbon derivatives, which can be absorbed through the lungs, gastrointestinal tract, and skin. These compounds can bind to AChE and red blood cell (RBC) and exchange the mentioned nonfunctional enzyme, leading to ACh overabundance at the NMJ and the neuronal synapses.[22,23] In addition, although pseudocholinesterase (PsCE) or plasma cholinesterase butyrylcholinesterase (BuChE), as well as neuropathy target esterase, are inhibited, there is no clear evidence regarding the clinical significance of the mentioned interactions.[24,25]

The use of OP compounds has reduced due to the improvement of carbamate insecticides over the last 10–20 years. Carbamate insecticides are associated with comparable toxicities; however, they have a strange mechanism of action. Contrary to OPs, carbamate compounds can be considered temporary cholinesterase inhibitors that are spontaneously hydrolyzed from the cholinesterase enzymatic site in 48 h and result in the same mortality rate and a shorter time of toxicity.[26]

Clinical Features

Clinical features are associated with the enzymatic conversion to active metabolites, agent lipophilicity, AChE inhibition rate, and absorption route of OP agents. Signs or symptoms can be normally observed within 3 h after oral or respiratory exposures, while the symptoms of dermal absorption toxicity might be delayed till 12 h. Lipophilic agents including fenthion, malathion, and dichlofenthion are linked with prolonged infection (>30 days) and behind schedule onset of symptoms (up to 5 days) that might be associated with the delayed redistribution from fat stores and fast adipose fat uptake.[26-28]

The manifestations consist of a) the expression of muscarinic overstimulation such as diarrhea, bronchospasm, urination, hypotension, bronchorrhea, salivation, lacrimation, miosis, vomiting, and hypotension; b) the expression of nicotinic overstimulation taking place in the sympathetic system such as mydriasis, sweating, hypertension, and tachycardia; c) the expression of nicotinic overstimulation within the central nervous system such as confusion, coma, respiratory failure, and agitation; and d) the expression of nicotinic overstimulation occurring in the NMJ such as fasciculation, paralysis, and muscle weakness.[29]

Defecation, Urination, Miosis, Bronchorrhea/Bronchospasm/Bradycardia, Emesis, Lacrimation, Salivation (DUMBELS) or Salivation, Lacrimation, Urination, Defecation, Gastric Emesis, Bronchorrhea, Bronchospasm, Bradycardia (SLUDGE/BBB) can be used to identify the muscarinic signs.[30]

Intermediate syndrome (IMS) as a particular neurological disorder occurs in 10–40% of poisonings 24–96 h following exposure. IMS is characterized using neurological findings such as cranial nerve abnormalities, decreased deep tendon reflexes, neck flexion weakness, respiratory insufficiency, and proximal muscle weakness.[31,32]

The proposed mechanism for IMS consists of numerous susceptibilities of various cholinergic receptors, desensitization or downregulation of postsynaptic ACh receptors, prolonged ache inhibition, oxidative strain-associated myopathy, failure of postsynaptic ACh release, inadequate oxime therapy, and muscle necrosis.[33] IMS has been diagnosed as a disease associated with NMJ, and its actual prevalence, etiology, and threat factors have not been defined certainly as the available studies are small scale and have not presented any rigorous and regular IMS definition.

Serum Albumin in OP Poisoning

Hypoalbuminemia is recognized as a negative consequence indicator and comprises morbidity, total medical institution and prolonged intensive care unit (ICU) remains, mortality in trauma, and extensive types of diseases.[34] Although the concentration of serum albumin can be regarded as the predictor of mortality in all age-range healthy individuals,[35] the potential role of the mentioned agent in predicting the mortality rate among OP-poisoned patients has not been investigated although serum albumin concentration is extensively available and is currently and routinely collected at medical institutes.

A number of studies have proposed that the binding of OP to albumin can result in destroying OP molecules and decreasing the amount of OP that is available for reacting with AChE.[36,37] Hydrolysis of OP by esterases can be considered a chief detoxification pathway for yielding a leaving group and a dialkyl phosphate that do not cause inhibition of AChE.[38] An *in vitro* study has indicated the esterase-like action of albumin with respect to the hydrolysis of metabolites of parathion and chlorpyrifos. This study demonstrated that albumin function is a degradation promoter of OP metabolites.[39]

The findings of preceding studies showed the significance of conducting more studies addressing the clinical role and the protective effects of serum albumin on OP poisoning as a probable treatment approach in this regard. Apparently, a relationship between mortality and serum albumin exists in OP poisoning. In addition, a good number of studies have reported hypoalbuminemia as a dose-based, reproducible, powerful, and impartial chance issue for undesired outcomes in individuals with various kinds of trauma and medical diseases.[40]

A study conducted by Lee JH *et al*.[41] revealed that there is a remarkably lower concentration of albumin after OP poisoning in non-surviving as compared with surviving patients. The monitoring of its concentration is recommended due to the cost-effectiveness of serum albumin tests and the observed strong association in this respect. This monitoring can be performed as a prognostic approach to recognize higher-risk patients following OP poisoning.

The pathophysiology explaining the mentioned association in patients suffering from OP poisoning cannot be specified. In addition, an inverse association has been reported between serum albumin and C-reactive protein (CRP) level that has already been proposed as a prognostic factor regarding OP poisoning.[42] However, it is still significant to devote due attention to the role of serum albumin concentration in the mortality rate following the adjustment of the CRP level. In other words, although inflammation might contribute to decreased concentrations of serum albumin, it cannot explain the relationship between mortality and serum albumin concentration. The mentioned finding might elucidate the involvement of albumin in a protection mechanism against OP toxicity. This involvement can also contribute to the serum albumin-related mortality rate. Estimations have shown the binding of about 1–2% of rat plasma albumin to biotin-labeled OP albumin that enjoys further bound to biotin-labeled OP than BuChE up to 1000 times. The mentioned binding level can be attributed to the remarkable abundance of albumin relative to BuChE within plasma. The findings revealed that there was no association between delta BuChE and delta albumin in patients with dichlorvos poisoning or chlorpyrifos. This finding may explain the potential protective effect of albumin by considering the OP type. This hypothesis suggests the competition between some OPs and biotinylated OP retailers for binding to albumin. A first rate function is performed by the structure of OP in specifying its affinity for albumin within the hydrolysis of OP metabolites.[39,43]

Diagnosis

Diagnosis of OP is chiefly based on clinical evidence. However, clinical features of cholinergic crisis may propose the potential for OP poisoning in case of no exposure or known ingestion. A decrease in the albumin concentration in the serum of poisoned patients alone or together with an increase in the serum level of CRP has a negative prognostic significance. Despite this, the determination of serum albumin levels in intoxicated patients during hospitalization has not yet been added to the measurement of butyrylcholinesterase (BChE) and AChE activity as a diagnostic tool.[22] Negative prognostic factors on admission were blood lactate, blood pH, alkalinity, Acute Physiology and Chronic Health Evaluation (APACHE) II score, blood lactate, 6 hours after admission, and length of hospital stay. BChE levels in blood plasma and AChE in whole blood were not among the negative prognostic markers and

seemed to be of diagnostic value only, as neither corresponded to the quantitative involvement of cholinergic synapses.[9]

If there is uncertainty in this respect, 0.01–0.02 mg/kg of atropine in children and 1 mg in adults can be used. The diagnosis of intoxication with an AChE inhibitor can be strongly supported following no symptoms or signs of the effect of anticholinergic after the atropine challenge.[20] At stages where oxime remedy is conjectured to be powerful, the therapeutic channel and the length of toxicity are noticeably various for diethyl and dimethyl compounds and accentuate the early start of oxime remedy, while diethyl compounds may indicate behind schedule toxicity and might need a prolonged treatment approach. Direct evaluation of RBC and AChE functions not only provides a toxicity level measure but is useful for comparing occupational or continual exposure. Moreover, despite their unavailability in most laboratories, the effectiveness of therapy can be evaluated using sequential assays.[44]

Prognosis

Numerous laboratory and clinical prognostic parameters have been employed for predicting a poor prognosis in adulthood age groups and a serious clinical course. In comparison with the poisoning severity scale, ICU-based clinical scoring systems such as the Simplified Acute Physiology Score (SAPS) II, the Mortality Prediction Model II, and the APACHE II have been reported to better predict the mortality in this respect.[45] The literature presents a single prospective study addressing the prognostic factors for patients poisoned with carbamate or acute OP and revealed an association between a poor prognosis and a Glasgow coma score (GCS) of less than 13. Moreover, they reported that GCS was as useful as the International Program on Chemical Safety Poison Severity Score.[46] However, due attention should be paid to the type of OP agent involved.

The results of the study by Minz *et al*.[47] indicated that by observing the decrease in AChE, OP poisoning and its severity can be confirmed. On the first day of admission, the average lipase, creatine kinase (CK), and amylase in mild poisoning were significantly lower than in moderate and severe poisoning. In addition, 24 and 26 patients with severe scores developed IMS and died, respectively. A positive correlation was observed between the severity of OP poisoning indicated by the Paediatric Observation Priority (POP) score and increased enzyme levels.

There are numerous laboratory and clinical indicators such as prolonged QT on electrocardiogram (ECG), amylase level, the GCS, body mass index, APACHE II score, CRP, red cell distribution width (RDW), blood pH, serum cholinesterase level, creatine phosphokinase, total leukocyte count, and systolic blood pressure that have been focused on in adult patients with acute OP intoxication to predict the clinical courses in this regard.[48,49]

Available evidence has revealed the effective role of GCSs in predicting the probable outcomes in OP.[50] For instance, Bilgin *et al*.[51] conducted a comparative study on the effectiveness of APACHE II score, SAPS II, and GCS to predict the risk of mortality in OP-poisoned patients. This study indicated that although all the mentioned scoring systems yielded identical results, implementation of the GCS was easier and superior as there was no need for complicated laboratory physiological parameters.[52] Similarly, Grmec *et al*.[53] proposed GCS as a predictive indicator for estimating mortality rate and respiratory failure.

The association between plasma AChE levels and the severity of intoxication has been a controversial issue stated in many studies.[53] Various studies have reported a lack of any correlation between the level of cholinesterase enzyme and the baseline clinical conditions of patients in OP.[54,55]

Chen *et al*.'s[56] study showed that there was an association between a high mortality rate and an increase in AChE levels within 48 hours following the treatment of OP intoxication. Serial measurements of serum AChE levels have been found useful in predicting the duration of mechanical ventilation, the duration of stay in ICUs, and the prognosis after OP intoxication.[57] Moreover, another study indicated the serum PsCE level at baseline as a predictor of treatment needs in ICU and serious intoxications in pediatric patients.[58]

Lactate as a byproduct of anaerobic metabolism has been recognized as a tissue hypoxia indicator.[59] Moreover, serum lactate levels have been highlighted as a predictive indicator.

Trzeciak *et al*.[60] focused on 100 patients and revealed the high specificity of lactate levels over 4 mmol/L in predicting mortality. Shapiro *et al*.[61] showed that the increase in lactate levels in high and moderate grades has resulted in 7.1- and 2.2-fold increases in mortality risk, respectively.

Many studies have investigated the serum glucose levels in OP-poisoned patients and have proposed the development of hyperglycemia due to catecholamines that are secreted from the adrenal medulla.[1] Moreover, the association between serum glucose levels and the severity of intoxication has been indicated. In addition, glucose levels were higher in the exitus cases as compared to the survivors.[62] Levy-Khademi *et al*.[63] conducted a retrospective study on children and reported a median glucose level of 130.5 mg/dL. Lifshitz *et al*.'s[64] study showed that there was an increased serum glucose level (155–280 mg/dL) in the majority of the studied cases.

Various sizes of erythrocyte distributions can be indicated by RDW as a hematological index.[65] The association of poor prognoses in different pathological conditions such as pancreatitis, pulmonary embolism, acute coronary syndrome, and heart failure with high RDW levels has been reported recently.[66,67] The mechanisms of action for increased levels of RDW are not well recognized; however, erythrocyte membrane deformation has been reported to be caused by chronic or acute inflammation.[68] Likewise, structure and size changes in

circulating erythrocytes might be due to oxidative stress and acute inflammation seen in OP intoxication.[69] The results of a clinical study showed that the RDW levels in OP-poisoned patients did not change with the ingestion of low doses of OPs. Another study suggested that RDW levels can be used as a valuable and available parameter to predict the prognosis in these patients. Moreover, the patients requiring ICU treatment, as compared with those not requiring similar treatment, had significantly higher mean RDW levels.[70]

Management

- **Atropine**

  Atropine as a competitive antagonist of the muscarinic ACh receptors in the peripheral and central nervous systems should be intravenously administered to rapidly maintain acceptable cardiorespiratory function, increase systolic blood pressure to more than 80 mmHg, and reverse bradycardia during the atropinization process. Concurrently, it improves oxygenation, reverses bronchospasm, and reduces bronchorrhea. The lack of crepitations and wheezing can be confirmed using auscultation. The outcomes of excessive atropine in antimuscarinic toxicity are absent bowel sounds, urinary retention, hyperthermia, ileus, tachycardia, and delirium. Toxicity and excess atropine management are not very significant during resuscitation; however, patients' condition should be improved considering the risk of cardiovascular collapse and accelerated agitation. There is a dearth of dose-response studies discovering the exact dosage routine for atropine. Recommendations varying noticeably between a dose of 23.4 mg over 8–1380 min and 75 mg over 25–4440 min have been provided in the literature review regarding atropine dose regimens.[71] Suitable resuscitation might be delayed for several hours using the majority of these regimens.[72] The findings revealed that the mean time of atropinization was reduced from 152 min to 24 min following this new regimen, which had a relationship with mortality rate, reduced from 22.5% to 8%.[72]

  A routine of sequentially doubling bolus doses is used to attain atropinization that would be titrated to effect. Following stabilization, the patients received the infusion starting at approximately 20–30% of the initial dose and titrated against impact. Then, bolus doses were used to be combined with it in case of being inadequate. Moreover, it was stopped or readministered with a lower dose in case of toxicity.[73]

  In some other studies, intravenous injection of atropine in a dose of 4–6 mg and repeating it in a dose of 2 mg until the bronchial secretions and saliva secretion decrease and the seizures stop are recommended, and its amount up to 24–48 mg on the first day has been considered probable.[74,75] In addition, the data of a retrospective study aimed at analyzing the maintenance dosage that was necessary to treat the muscarinic features of severe OP poisoning showed that a plasma concentration of S-hyoscyamine of about 5 nmol L-1 was sufficient when RBC-AChE was between 10% and 30% normal. The dose of atropine required to maintain this concentration was about 0.35 mg/h. Higher doses (above 2 mg/h) were required only when RBC-AChE was completely inhibited, whereas atropine was generally ineffective when RBC-AChE activity exceeded 30% of normal. Therefore, RBC-AChE seems to be a suitable surrogate parameter that allows an approximate estimation of the maintenance dose of atropine.[76,77]

- **Oxime AChE reactivators**

  The use of pralidoxime for treating OP insecticides refers back to the late 1950s and was first employed for treating highly toxic WHO class I insecticides. As a marked clinical improvement was observed, its administration has been highly suggested.[78] The chloride salt is presently the most widely employed oxime across the world.[79] Germany developed obidoxime as the second oxime in the 1960s. The use of human red cell AChE, as compared with pralidoxime, within *in vitro* reactivation experiments indicated its significant effect.[44] Although formal comparative RCTs of obidoxime are not available, reactivation of red cell AChE and its administration are found to be associated with poisoned patients.[80] In the Iranian context, obidoxime (8 mg/kg loading then 2 mg/kg/h infusion) was used for 22 patients poisoned with OP insecticide. Three patients had liver toxicity, and two patients died. Three and two patients pronounced liver toxicity and died, respectively.[23]

  It should be noted that obidoxime loading doses of 250 mg by the administration of 750 mg/24 h did not lead to hepatotoxicity.[81] Although some other oximes such as HLö-7, HI-6, and trimedoxime have been developed, they are not recommended for extensive clinical use. The mentioned point can be attributed to the fact that their development has concentrated on OP nerve agent poisoning rather than the common OP insecticide poisoning within developed countries.[82]

- **Sodium Bicarbonate (NaHCO3)**

  $NaHCO_3$ has been recommended for blood alkalinization for a long time; however, the precise mechanism of the potential benefit is still indefinite and might consist of a direct effect on the neuromuscular function, the clearance of OP using pH-mediated hydrolysis, or the increased efficacy of oximes.[26] Although a few small-scale randomized controlled trials (RCTs) have been found to be beneficial, large-scale RCTs have not been performed. Moreover, no benefits were reported by a Cochrane review.[38,83]

  According to the results of Roberts *et al*.'s[84] study, intravenous administration of $NaHCO_3$ at a dose of 5 mEq/kg for 1 hour, followed by 5–6 mEq/kg daily until recovery or death, maintains arterial pH between 7.45 and 7.55. There was no effect on OP pesticide poisoning, but the injection of higher doses of NaHCO3 seems to be beneficial for the treatment of OP-poisoned patients.[24]

- **CCB drugs**
  The administration of CCB has been reported in three small-scale studies focusing on patients with cardiac dysrhythmias such as cardiac arrests. $MgSO_4$ and CCB have been used in the first study without providing details of patients.[85] In the second study, diltiazem (1–3 mg/kg intravenous (IV) over 30–150 min) for a sinus tachycardia of about 165/min was used for nine OP-poisoned patients.[86] The heart rate decreased in eight patients, and two died. The third study used an unnamed CCB for treating seven OP-poisoned patients with cardiac arrests 3–5 days after their poisoning and two of them died.[87] CCB can reduce synaptic ACh release and may reduce the risk of ventricular tachycardia in patients with nicotine-induced tachycardia. In addition, some studies have mentioned its role in improving neuromuscular function and reducing mortality.[88]
  Moreover, two observational studies focused on CCB as an OP antidote in OP-poisoned patients and neither examined the potential role of CCB nor presented any information regarding the mortality rate and ventilation/intubation after the treatment. However, the standard clinical use for injury and cardiac dysrhythmias was addressed in these studies.[89,90] Lower serum CK, lactate dehydrogenase (LDH) activity, and aspartate transaminase as well as fewer pathological ECG changes including atrioventricular block, QT prolongation, and ST depression were associated with verapamil treatment. Verapamil administration (5 mg IV every 6 h for 3 d and then 40 mg orally three times daily for 1 week) in 45 patients with OP insecticide poisoning, as compared with conventional treatment provided for 44 patients, resulted in identical effects on creatine kinase-myocardial band (CK-MB), CK, and lactate dehydrogenase (LDH) activity.[85]
- **Magnesium Sulfate**
  $MgSO_4$ can be regarded as an ACh release inhibitor in peripheral parasympathetic and sympathetic synapses and the central nervous system. The mentioned drug can lead to the inhibition of calcium channels within presynaptic nerve terminals, which results in the ACh release and the hydrolysis increase in some pesticides. In addition, it decreases arrhythmias that have an association with atropine and OP compound poisoning (OPCP), acts upon the NMDA receptor, leads to the weakness of neuromuscles in the peripheral nervous system, and decreases overstimulation by OPCP within the central nervous system.[19,91]

The review of the literature indicated that only a few studies have assessed the role of $MgSO_4$ in OPCP patients' outcomes and ICU stays. The results of a study examining the effect of administering 4 g of $MgSO_4$ to OPCP patients within 24 h of ICU admission showed that the length of ICU stay, the intubation requirement, and the need for atropine decreased, while the duration of the mechanical ventilation and the mortality rate did not differ significantly between the groups.[92]

The majority of OPCP symptoms and signs originated from the overstimulation of the muscarinic receptor. Reduced bronchial and neuromuscular dysfunction as well as central movement are caused by severe acute poisoning and result in respiratory arrest and patient mortality over 30 minutes of ingestion.[93] Neuromuscular weakness among non-survivors with acute toxicity in three types of paralysis including type 1 paralysis with weakness within 24 h, type 2 paralysis with weakness after 24 h to 2 weeks (IMS), and type 3 paralysis after 2 weeks (OP-induced polyneuropathy) is classified.[94,95] The therapeutic value of oximes can be observed in neuromuscular recovery; however, there are still controversies regarding their effects on the reactivation of the AChE enzyme. Its timing, dosage, harmfulness, and effectiveness have been addressed in some recent studies.[96,97] Moreover, some ongoing studies evaluate the effectiveness of lipid emulsions, OP hydrolases nicotinic receptor antagonists, beta-adrenergic agonists, magnesium, and fresh frozen plasma (FFP) on OPCP management.[98] Moreover, magnesium was successfully used for managing cardiac arrhythmias caused by OPCP.[99] One clinical study revealed the reversal of neuroelectrophysiological deficits caused by OPCP. The length of stay and mortality reduced following the administration of 4 g of $MgSO_4$ within the first 24 hours of hospitalization due to OPCP.[100-102] The possible effect of magnesium on patients' need for atropine is a controversial issue.[103] However, patients receiving magnesium required a significantly lower dose of atropine. Furthermore, the need for mechanical ventilation and intubation fluctuates between 50 and 88%, which was determined by the poisoning severity.[96] Reversal of NMJ effects of OP exposure was reported regarding four patients in a small-scale neurophysiological study focusing on $MgSO_4$; however, patient's clinical status was not improved.[104] The mentioned patients were studied 2–9 days after exposure and did not receive treatment instantly after their hospitalization. The administration of $MgSO_4$ for managing hypertonic uterine contractions and cardiac dysrhythmias was described in three case reports, none of which examined the $MgSO_4$ effect on OP poisoning generally.[15,88,105]

$MgSO_4$ at a dose of 4 g/day IV for the first 24 hours after admission is the most widely investigated dose of $MgSO_4$ and does not require intensive monitoring of Mg^{2+} concentration considering its routine administration and efficacy for preventing cardiac dysrhythmias. However, despite recommendations suggesting the higher benefit of 4 g $MgSO_4$ doses every 4 h, a bolus dose of 4 g over 1 h followed by an infusion of 1 g/h for 24 h was tested subsequently by another RCT.[106,107] Although its effectiveness was not examined in the study due to the small size of its sample, no toxic concentrations of Mg^{2+} (>2.5 mmol/L with severe effects occurring at concentrations >7 mmol/L) were noticed.[108]

Other Agents

A number of animal models have used numerous other agents for managing OP poisoning. ACh synthesis can be decreased by alpha-2 adrenergic receptor agonists such as clonidine, which can be released in presynaptic junctions. However, its efficacy has not been confirmed in human studies. Antioxidants (such as vitamins C and E) have been proposed to have a therapeutic effect in OP poisoning by increasing lipid peroxidation and thiobarbituric reactive substances following chronic, sub-chronic, and acute exposure.[106,109]

Newer Therapies in Management of OP Poisoning

- K-oxime
  The development of effective broad-spectrum AChE activators has been addressed over recent years. Numerous compounds have been developed in this respect, and K-oximes appear to be the most beneficial ones. *In vitro* and *in vivo* studies have examined naloxone, diisopropyl fluorophosphate, and paraoxon, which, in comparison with pralidoxime, revealed the potential to significantly reactivate K-75, K-48, and K-27. Considering the present controversies with regard to the therapeutic efficacy of pralidoxime, more novel oximes can be a promising treatment method for OP poisoning.[110]
- Hemoperfusion
  OP pesticides, which are lipid-soluble macromolecular substances, have the ability to bind to proteins effortlessly. Repeated hemoperfusion has been recommended to swiftly alleviate the intoxication symptoms and reduce pertinent complications as it results in high efficacy for clearing plasma or lipid-soluble protein-bound toxins. Bo conducted a recent study comparing single versus repeated hemoperfusion for treating OP and showed the higher efficacy of repeated hemoperfusion.[111]
- FFP
  Biological scavengers including albumin or FFP through scavenging of free OPs have been recommended as a beneficial treatment. The results of some studies indicated that the level of 2-BuChE would increase as a result of FFP treatment in OP-poisoned patients. This finding suggests that this treatment may moderate mortality and syndrome development.[112] However, the results of another study did not indicate the significant effectiveness of treatment with albumin or FFP despite significantly increased BuChE concentrations with FFP.[113]

Conclusions and Recommendations

The fundamental principles of OP treatment and novel medications have been presented in recent studies. However, a number of factors including the employed treatment strategies, the hospitalization times, and the type of insecticides ingested might affect the effectiveness of medications among all or some subgroups of patients. The present review study figured out that serum glucose, serum lactate, and serum AChE levels at baseline, as well as the GCS, are helpful in prognosis and are good predictors of the presence of a serious intoxication. Despite the lack of definite evidence regarding the mechanism of an effect for CCB and $MgSO_4$, the benefits of CCB can be considered to be preservative to atropine. However, it seems that the CCB-inhibited voltage-dependent Ca2+ channels are not taking part in increasing cytosolic calcium level following exposure to OP. In addition, concentrations of intracellular Ca2+ and the release of AChE might be increased by its compounds by inhibiting Ca2+ adenosine triphosphatase (ATPase), which is an enzyme responsible for removing cytosolic Ca2+ by pumping it into an extracellular medium or sequestrating it into intracellular stores such as mitochondria. The increase in the concentration of serum $MgSO_4$ from 1 to 4 mM is anticipated to decrease the release of the evoked neurotransmitter at NMJs by 10–20%; however, the decrease in muscle contraction and functional neuromuscular transmission should not be significantly affected because of its effects on the end-plate depolarization of NMJs and the high safety factor for the transmitter release. The dual effect of Mg2+ ions on L-type (and possibly N-type) Ca channels can be explained as follows: a) blocking the L-type Ca2+ channels at a millimolar concentration and b) facilitating the L-type Ca2+ channels at lower (sub-micromolar) concentrations of $MgSO_4$. However, the subtypes of Ca2+ channels are not believed to significantly participate in the fast nerve-evoked transmitter release. $MgSO_4$ might act extracellularly to decrease the effectiveness of the potentials of intracellular calcium release within the presynaptic active zones or might have competition with Ca2+ for intracellular binding sites on the calcium-sensing synaptotagmin. More effective treatments can be proposed for severe OP poisonings by performing further studies in this regard. The most beneficial management modality seems to be prevention. Pesticide control and appropriate legislation are suggested for preventing intentional, accidental, and occupational poisonings in developing countries.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gündüz E, Dursun R, Icer M, Zengin Y, Güllü M, Durgun H, *et al*. Factors affecting mortality in patients with organophosphate poisoning. J Pak Med Assoc 2015;65:967-72.
2. Eddleston M. Poisoning by pesticides. Medicine 2020;48:214-7.
3. Xu B, Zeng W, Chen F, Lin G, Wang M, Ding J, *et al*. Clinical characteristics and early prediction of mortality risk in patients with acute organophosphate poisoning-induced shock. Front Med 2023;9:990934.
4. World Health Organization. Suicide Worldwide in 2019: Global Health Estimates; World Health Organization: Geneva, Switzerland; 2021. ISBN 9789240026643.

5. Centers for Disease Control and Prevention. Injury Prevention & Control. Available from: https://www.cdc.gov/injury/index.html. [Last accessed on 2022 Jul 09].
6. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet 2008;371:597-607.
7. Young RA, Watson A. Organophosphate nerve agents. InHandbook of Toxicology of Chemical Warfare Agents 2020:97-126.
8. Bajgar J. Organophosphates nerve agent poisoning: Mechanism of action, diagnosis, prophylaxis, and treatment. Adv Clin Chem 2004;38:151-216.
9. Eddleston M, Chowdhury FR. Organophosphorus poisoning: The wet opioid toxidrome. Lancet 2021;397:175-7.
10. Ruckart PZ, Kakolewski K, Bove FJ, Kaye WE. Long-term neurobehavioral health effects of methyl parathion exposure in children in Mississippi and Ohio. Environ Health Perspect 2004;112:46-51.
11. Deshpande LS, Blair RE, Phillips KF, DeLorenzo RJ. Role of the calcium plateau in neuronal injury and behavioral morbidities following organophosphate intoxication. Ann N Y Acad Sci 2016;1374:176-83.
12. Karami-Mohajeri S, Nikfar S, Abdollahi M. A systematic review on the nerve-muscle electrophysiology in human organophosphorus pesticide exposure. Hum Exp Toxicol 2014;33:92-102.
13. Eddleston M, Mohamed F, Davies JOJ, Eyer P, Worek F, Sheriff MH, *et al*. Respiratory failure in acute organophosphorus pesticide self-poisoning. QJM 2006;99:513-22.
14. Hulse EJ, Davies JO, Simpson AJ, Sciuto AM, Eddleston M. Respiratory complications of organophosphorus nerve agent and insecticide poisoning. Implications for respiratory and critical care. Am J Respir Crit Care Med 2014;190:1342-54.
15. Abdolrazaghnejad A, Banaie M, Tavakoli N, Safdari M, Rajabpour-Sanati A. Pain management in the emergency department: A review article on options and methods. Adv J Emerg Med 2018;2e45.
16. Candole CA, Douglas WW, Evans CL, Holmes R, Spencer KE, Torrance RW, *et al*. The failure of respiration in death by anticholinesterase poisoning. Brit J Pharmacol 1953;8:466-75.
17. Abdolrazaghnejad A, Banaie M, Tavakoli N, Safdari M, Rajabpour-Sanati A. Pain Management in the Emergency Department: A Review Article on Options and Methods. Adv J Emerg Med. 2018;2:e45.
18. Sharafkhah M, Abdolrazaghnejad A, Zarinfar N, Mohammadbeigi A, Massoudifar A, Abaszadeh S. Safety and efficacy of N-acetyl-cysteine for prophylaxis of ventilator-associated pneumonia: A randomized, double blind, placebo-controlled clinical trial. Med Gas Res 2018;8:19.
19. Eddleston M, Chowdhury FR. Pharmacological treatment of organophosphorus insecticide poisoning: The old and the (possible) new. Br J Clin Pharmacol 2016;81:462-70.
20. Abedin MJ, Sayeed AA, Basher A, Maude RJ, Hoque G, Faiz MA. Open-label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. J Med Toxicol 2012;8:108-17.
21. Blumenberg A, Benabbas R, deSouza IS, Conigliaro A, Paladino L, Warman E, *et al*. Utility of 2-pyridine aldoxime methyl chloride (2-PAM) for acute organophosphate poisoning: A systematic review and meta-analysis. J Med Toxicol 2018;14:91-8.
22. Ramadori GP. Organophosphorus poisoning: Acute respiratory distress syndrome (ARDS) and cardiac failure as cause of death in hospitalized patients. Int J Mol Sci 2023;24:6658.
23. Khurana D, Prabhakar S. Organophosphorus intoxication. Arch Neurol 2000;57:600-2.
24. Balali-Mood M, Saber H. Recent advances in the treatment of organophosphorous poisonings. Iran J Med Sci 2012;37:74-91.
25. Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in acute organophosphorus pesticide poisoning: A systematic review of clinical trials. QJM 2002;95:275-83.
26. Rotenberg M, Shefi M, Dany S, Dore I, Tirosh M, Almog S. Differentiation between organophosphate and carbamate poisoning. Clin Chim Acta 1995;234:11-21.
27. Robb EL, Baker MB. Organophosphate toxicity. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470430/. [Last accessed on on 2022 May 01].
28. Eddleston M, Eyer P, Worek F, Mohamed F, Senarathna L, von Meyer L, *et al*. Differences between organophosphorus insecticides in human self-poisoning: A prospective cohort study. Lancet 2005;366:1452-9.
29. Kumar A, Margekar SL, Margekar P, Margekar V. Recent advances in management of organophosphate & carbamate poisoning. Indian Journal of Medical Specialities. 2018;9:154-9.
30. Sidell FR. Clinical effects of organophosphorus cholinesterase inhibitors. J Appl Toxicol 1994;14:111-3.
31. Indira M, Andrews MA, Rakesh TP. Incidence, predictors, and outcome of intermediate syndrome in cholinergic insecticide poisoning: A prospective observational cohort study. Clin Toxicol (Phila) 2013;51:838-45.
32. Karalliedde L, Baker D, Marrs TC. Organophosphate-induced intermediate syndrome: Aetiology and relationships with myopathy. Toxicol Rev 2006;25:1-14.
33. Yang CC, Deng JF. Intermediate syndrome following organophosphate insecticide poisoning. J Chin Med Assoc 2007;70:467-72.
34. Noh E, Moon JM, Chun BJ, Cho YS, Ryu S, Kim D. The clinical role of serum albumin in organophospate poisoning. Basic Clin Pharmacol Toxicol 2021;128:605-14.
35. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and clinical significance. JPEN J Parenter Enteral Nutr 2019;43:181-93.
36. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: Is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319-34.
37. Fulks M, Stout RL, Dolan VF. Albumin and all-cause mortality risk in insurance applicants. J Insur Med 2010;42:11-7.
38. Roberts D, Buckley NA. Alkalinisation for organophosphorus pesticide poisoning. Cochrane Database Syst Rev 2005;1:CD004897.
39. Peeples ES, Schopfer LM, Duysen EG, Spaulding R, Voelker T, Thompson CM, *et al*. Albumin, a new biomarker of organophosphorus toxicant exposure, identified by mass spectrometry. Toxicol Sci 2005;83:303-12.
40. Kim SY, Lee RK, Kim DH, Kim T, Lee SH, Jeong JH, *et al*. Hypoalbuminemia as a predictor of 30-day mortality in patients with acute organophosphate insecticide poisoning. J Korean Soc Clin Toxicol 2017;15:11-6.
41. Lee SB, Kang C, Kim DH, Kim T, Lee SH, Jeong JH, *et al*. Base deficit is a predictor of mortality in organophosphate insectcide poisoning. Hum Exp Toxicol 2018;37:118-24.
42. Wu X, Xie W, Cheng Y, Guan Q. Severity and prognosis of acute organophosphorus pesticide poisoning are indicated by C-reactive protein and copeptin levels and APACHE II score. Exp Ther Med 2016;11:806-10.
43. Li W, Xiao H, Wu H, Xu X, Zhang Y. Organophosphate pesticide exposure and biomarkers of liver injury/liver function. Liver Int 2022;42:2713-23.
44. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev 2003;22:165-90.
45. Peter JV, Thomas L, Graham PL, Moran JL, Abhilash KP, Jasmine S, *et al*. Performance of clinical scoring systems in acute organophosphate poisoning. Clin Toxicol (Phila) 2013;51:850-4.
46. Davies JO, Eddleston M, Buckley NA. Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. QJM 2008;101:371-9.
47. Minz NT, Singh SC, Jena P, Patro PK. Correlation of serum amylase, lipase, and creatine kinase with severity of organophosphate poisoning - A cohort study. J Clin Diagn Res 2021;15:19.
48. Bateman DN. Paracetamol poisoning: Beyond the nomogram. Br J Clin Pharmacol 2015;80:45-50.
49. Groothuis-Oudshoorn K, Buuren SV. {mice}: Multivariate imputation by chained equations in R. J Stat Software 2011;45:1-67.
50. Cander B, Dur A, Yildiz M, Koyuncu F, Girisgin AS, Gul M, *et al*. The prognostic value of the Glasgow coma scale, serum acetylcholinesterase and leukocyte levels in acute organophosphorus poisoning. Ann Saudi Med 2011;31:163-6.
51. Bilgin TE, Camdeviren H, Yapici D, Doruk N, Altunkan Z, Oral U. The comparison of the efficacy of scoring systems in organophosphate poisoning. Toxicol Ind Health 2005;21:141-6.

52. Coskun R, Gundogan K, Sezgin GC, Topaloglu US, Hebbar G, Guven M, *et al*. A retrospective review of intensive care management of organophosphate insecticide poisoning: Single center experience. Niger J Clin Pract 2015;18:644-50.
53. Grmec S, Mally S, Klemen P. Glasgow Coma Scale score and QTc interval in the prognosis of organophosphate poisoning. Acad Emerg Med 2004;11:925-30.
54. Sepahi S, Gerayli S, Delirrad M, Taghavizadeh Yazdi ME, Zare-Zardini H, Bushehri B, Ghorani-Azam A. Biochemical responses as early and reliable biomarkers of organophosphate and carbamate pesticides intoxication: A systematic literature review. Journal of Biochemical and Molecular Toxicology. 2023;37:e23285.
55. Aygun D. Diagnosis in an acute organophosphate poisoning: Report of three interesting cases and review of the literature. Eur J Emerg Med 2004;11:55-8.
56. Chen HY, Wang WW, Chaou CH, Lin CC. Prognostic value of serial serum cholinesterase activities in organophosphate poisoned patients. Am J Emerg Med 2009;27:1034-9.
57. Manu MS, Prashant V, Akila P, Suma MN, Basavanagowdappa H. A retrospective analysis of serial measurement of serum cholinesterase in acute poisoning with organophosphate compounds. Toxicol Int 2012;19:255-9.
58. Açıkgöz M. Evaluation of clinical and laboratory prognostic risk factors in organophosphate or carbamate-poisoned pediatric patients. Eurasian J Emerg Med 2021;20:71-8.
59. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. Am J Surg 2003;185:485-91.
60. Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, *et al*. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 2007;33:970-7.
61. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Libson A, Wolfe RE, *et al*. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med 2005;45:524-8.
62. Panda S, Nanda R, Mangaraj M, Rathod PK, Mishra PK. Glycemic status in organophosphorus poisoning. J Nepal Health Res Counc 2015;13:214-9.
63. Levy-Khademi F, Tenenbaum AN, Wexler ID, Amitai Y. Unintentional organophosphate intoxication in children. Pediatr Emerg Care. 2007;23:716-8.
64. Lifshitz M, Rotenberg M, Sofer S, Tamiri T, Shahak E, Almog S. Carbamate poisoning and oxime treatment in children: A clinical and laboratory study. Pediatrics 1994;93:652-5.
65. Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/undifferentiated colitis. Dig Dis Sci 2008;53:2521-3.
66. Kaya A, Isik T, Kaya Y, Enginyurt O, Gunaydin ZY, İscanli MD, *et al*. Relationship between red cell distribution width and stroke in patients with stable chronic heart failure: A propensity score matching analysis. Clin Appl Thromb Hemost 2015;21:160-5.
67. Montagnana M, Cervellin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clin Chem Lab Med 2011;50:635-41.
68. Şenol K, Saylam B, Kocaay F, Tez M. Red cell distribution width as a predictor of mortality in acute pancreatitis. Am J Emerg Med 2013;31:687-9.
69. Arslan B, Akdağ D, Ünlü N, Arslan A, Açık V. The prognostic value of red cell distribution width for in-hospital mortality in patients with methanol poisoning. Human & Experimental Toxicology. 2021;40:196-202.
70. Al-Sarar AS, Abo Bakr Y, Al-Erimah GS, Hussein HI, Bayoumi AE. Hematological and biochemical alterations in occupationally pesticides-exposed workers of Riyadh Municipality, Kingdom of Saudi Arabia. Res J Environ Toxicol 2009;3:179-85.
71. Eddleston M, Buckley NA, Checketts H, Senarathna L, Mohamed F, Sheriff MH, Dawson A. Speed of initial atropinisation in significant organophosphorus pesticide poisoning-A systematic comparison of recommended regimens. J Toxicol Clin Toxicol 2004;42:865-75.
72. Connors NJ, Harnett ZH, Hoffman RS. Comparison of current recommended regimens of atropinization in organophosphate poisoning. J Med Toxicol 2014;10:143-7.
73. Aaron CK. Organophosphates and carbamates. In: Ford MD, Delaney KA, Ling LJ, Erickson T, editors. Clinical Toxicology. Philadelphia, PA: W. B. Saunders Company; 2001. p. 819-28.
74. Husain K, Ansari RA, Ferder L. Pharmacological agents in the prophylaxis/treatment of organophosphorous pesticide intoxication. Indian J Exp Biol 2010;48:642-50.
75. Sungur M, Güven M. Intensive care management of organophosphate insecticide poisoning. Crit 2001;5:1-5.
76. Thiermann H, Steinritz D, Worek F, Radtke M, Eyer P, Eyer F, *et al*. Atropine maintenance dosage in patients with severe organophosphate pesticide poisoning. Toxicol Lett 2011;206:77-83.
77. Eddleston M. Novel clinical toxicology and pharmacology of organophosphorus insecticide self-poisoning. Annu Rev Pharmacol Toxicol 2019;59:341-60.
78. Johnson MK, Jacobsen D, Meredith TJ, Eyer P, Heath AJ, Ligtenstein DA, *et al*. Evaluation of antidotes for poisoning by organophosphorus pesticides. Emerg Med 2000;12:22-37.
79. Eyer P, Eddleston M, Thiermann H, Worek F, Buckley NA. Are we using the right dose? A tale of mole and gram. Br J Clin Pharmacol 2008;66:451-2.
80. Thiermann H, Mast U, Klimmek R, Eyer P, Hibler A, Pfab R, *et al*. Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. Hum Exp Toxicol 1997;16:473-80.
81. Balali-Mood M, Shariat M. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. J Physiol Paris 1998;92:375-8.
82. Eyer F, Worek F, Eyer P, Felgenhauer N, Haberkorn M, Zilker T, *et al*. Obidoxime in acute organophosphate poisoning: 1-clinical effectiveness. Clin Toxicol (Phila) 2009;47:798-806.
83. Motawei SM, Elbaiomy AA, Abou-ElWafa HS. Sodium bicarbonate and N-Acetyl cysteine in organophosphorus poisoning cases of different severity: A randomized controlled clinical trial. Mansoura Med J 2022;51:124-35.
84. Roberts DM, Dawson AH, Hittarage A, Jeganathan K, Sheriff MH, Buckley NA. Plasma alkalinization for acute organophosphorus poisoning - Is it a reality in the developing world? Clin Toxicol (Phila) 2007;45:90-1.
85. Brvar M, Chan MY, Dawson AH, Ribchester RR, Eddleston M. Magnesium sulfate and calcium channel blocking drugs as antidotes for acute organophosphorus insecticide poisoning - A systematic review and meta-analysis. Clin Toxicol 2018;56:725-36.
86. Zhang JY, Zhao JY, Zhao CL. Clinical observation of diazepam and verapamil in preventing heart damage caused by acute organophosphate poisoning. J Occup Health Damage 2001;16:13-14.
87. Fang JL, Shao QP, Qian XQ. Application of calcium channel blocker in rescue of severe organophosphate pesticide poisoning. Chin Med Fact Mine, 1997;3:201-2.
88. Basher A, Rahman SH, Ghose A, Arif SM, Faiz MA, Dawson AH. Phase II study of magnesium sulfate in acute organophosphate pesticide poisoning. Clin Toxicol (Phila) 2013;51:35-40.
89. Tao XS, Zheng JQ. The experience of using diltiazem hydrochloride for sinus tachycardia in nine cases of severe organophosphate pesticide poisoning. Fujian Med J 2010;32:138-9.
90. Ru XW. Study on the protective effect of verapamil on myocardial injury induced by organophosphate pesticide poisoning. Cent Plains Med J 2003;30:21-2.
91. Singh G, Khurana D. Neurology of acute organophosphate poisoning. Neurol India 2009;57:119-25.
92. Noshad H, Ansarin K, Ardalan MR, Ghaffari AR, Safa J, Nezami N. Respiratory failure in organophosphate insecticide poisoning. Saudi Med J 2007;28:405-7.
93. Anand S, Singh S, Nahar Saikia U, Bhalla A, Paul Sharma Y, Singh D. Cardiac abnormalities in acute organophosphate poisoning. Clin Toxicol (Phila) 2009;47:230-5.
94. Karki P, Ansari JA, Bhandary S, Koirala S. Cardiac and electrocardiographical manifestations of acute organophosphate poisoning. Singapore Med J 2004;45:385-9.
95. Saadeh AM, Farsakh NA, al-Ali MK. Cardiac manifestations of acute carbamate and organophosphate poisoning. Heart 1997;77:461-4.

96. Lee P, Tai DY. Clinical features of patients with acute organophosphate poisoning requiring intensive care. Intensive Care Med 2001;27:694-9.
97. Brahmi N, Mokline A, Kouraichi N, Ghorbel H, Blel Y, Thabet H, *et al*. Prognostic value of human erythrocyte acetyl cholinesterase in acute organophosphate poisoning. Am J Emerg Med 2006;24:822-7.
98. Bobba R, Venkataraman BV, Pais P, Joseph T. Correlation between the severity of symptoms in organophosphorus poisoning and cholinesterase activity (RBC and plasma) in humans. Indian J Physiol Pharmacol 1996;40:249-52.
99. Eddleston M, Eyer P, Worek F, Sheriff MH, Buckley NA. Predicting outcome using butyrylcholinesterase activity in organophosphorus pesticide self-poisoning. QJM. 2008;101:467-74.
100. Atri A, Chang MS, Strichartz GR. Cholinergic pharmacology. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW, editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2011. p. 110-31.
101. Zandona A, Katalinić M. Nicotinic acetylcholine receptors: Diversity and physiological importance for neurodegenerative disorders and development of organophosphate antidotes. Period Biol 2020;121:115-28.
102. Williamson J, Singh T, Kapur J. Neurobiology of organophosphate-induced seizures. Epilepsy Behav 2019;101:106426.
103. Abrams P, Andersson KE, Buccafusco JJ, Chapple C, de Groat WC, Fryer AD, *et al*. Muscarinic receptors: Their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol 2006;148:565-78.
104. Sengupta S, Chakravarty C. Organophosphorus poisoning. Yearb Anesthesiol. 2019;8:98.
105. Nel L, Hatherill M, Davies J, Andronikou S, Stirling J, Reynolds L, *et al*. Organophosphate poisoning complicated by a tachyarrhythmia and acute respiratory distress syndrome in a child. J Paediatr Child Health 2002;38:530-2.
106. Raghuveer P. Effect of Vitamin E and Magnesium Sulphate in Prognosis of Op Poisoning. Doctoral dissertation. Rajiv Gandhi University of Health Sciences (India); 2019.
107. Ranjbar A, Solhi H, Mashayekhi FJ, Susanabdi A, Rezaie A, Abdollahi M. Oxidative stress in acute human poisoning with organophosphorus insecticides; A case control study. Environ Toxicol Pharmacol 2005;20:88-91.
108. Philomena J, Sathi V, Prathiba P. A case control study of intravenous magnesium sulphate in treatment of acute organophosphate poisoning. J Evol Med Dent Sci 2016;5:2290-94.
109. Narang U, Narang P, Gupta O. Organophosphorus poisoning: A social calamity. J Mahatma Gandhi Inst Med Sci 2015;20:46.
110. Worek F, Thiermann H, Wille T. Organophosphorus compounds and oximes: A critical review. Arch Toxicol 2020;94:2275-92.
111. Bo L. Therapeutic efficacies of different hemoperfusion frequencies inpatients with organophosphate poisoning. Eur Rev Med Pharmacol Sci 2014;18:3521-3.
112. Gheshlaghi F, Akafzadeh Savari M, Nasiri R, Wong A, Feizi A, Reza Maracy M, *et al*. Efficacy of fresh frozen plasma transfusion in comparison with conventional regimen in organophosphate poisoning treatment: A meta-analysis study. Crit Rev Toxicol 2020;50:677-84.
113. Güven M, Sungur M, Eser B, Sarı İ, Altuntaş F. The effects of fresh frozen plasma on cholinesterase levels and outcomes in patients with organophosphate poisoning. J Toxicol Clin Toxicol 2004;42:617-23.