CPK MB levels in Organophosphorous Compound Poisoning

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Abstract
Organophosphorous compounds are one of the most commonly used compounds used for suicidal intentions in the developing countries. Organophosphates by their action at muscarinic and nicotinic receptors can have a myriad of presenting symptoms. Here we describe a fatal case of phorate (organophosphorus) toxicity manifesting with hypothermia and cardiotoxicity. CPK, CPK-MB, and Troponin I in acute organophosphorus poisoning, to analyse the correlation between these biochemical parameters and serum acetylcholinesterase levels and to assess the validity of these biochemical parameters in prediction of severity and prognosis in OP poisoning. CPK-MB levels are frequently raised among the OPC poisoning patients and ECG changes are also frequently observed among the OPC poisoning patients. Researchers tend to understand the association between CPK-MB levels and ECG changes to predict prognosis in OPC poisoning patients presenting in the department of emergency. Laboratory evidence of OP poisoning is usually confirmed by measuring the decreases in the blood and erythrocyte cholinesterase activities. Rise in CPK, CPK-MB, Troponin I and ALT indicate the severity of OP poisoning and is also statistically significant to predict the prognosis of the patient. There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like creatine phosphokinase (CPK).

Keywords: Creatinine phosphokinase-MB, Electrocardiographic changes, Organophosphorus poisoning.

Introduction
Organophosphorus compounds are possibly the widely used insecticides across the globe. These are irreversible cholinesterase inhibitors with potential human toxicity[1]. OP compound poisoning is an important preventable public health problem in developing countries. Though accidental poisoning can occur following exposure or inhalation, serious poisoning often follows suicidal ingestion[2]. One of the most important steps in green revolution is pesticides. Pesticides are a class of toxic substances that are intentionally released into the environment for the greater good it does that exceeds their toxicological concerns. In the developing world, Poisoning is a common method of suicide[3]. Pesticide poisoning is a major health hazard in the developing world[4]. Millions of people are exposed to these dangerous chemicals because of the occupational hazards and also because of unsafe storage practices[5]. A high incidence of mortality has been reported in past, and is
attributed to delay in diagnosis and improper treatment\textsuperscript{[6]}. More than three fourth of pesticide related hospital admissions are due to organophosphorus compounds and are associated with lethal human effects\textsuperscript{[7]}. WHO published that eight lakh forty nine thousand people died due to pesticide poisoning yearly\textsuperscript{[8]}. However it is the deliberate self poisoning that causes majority of the deaths and a difficult health strategy to manage among health services, especially in Asia. According to World health organization report, about three million cases of pesticide poisoning occur every year worldwide and most of them are in Asia, among which 50\% of them are organophosphate poisoning. Organophosphate compounds are irreversible inhibitors of the enzyme acetyl cholinesterase, binding to the esteric site of the enzyme. Organophosphorus compounds inhibit acetyl cholinesterase and butyryl cholinesterase enzymes resulting in excess acetylcholine in the neuromuscular junction causing overstimulation at the cholinergic synapses\textsuperscript{[9]}. They inhibit both cholinesterase and pseudo cholinesterase activity. This inhibition causes accumulation of acetylcholine at synapses with resultant overstimulation of neurotransmission.\textsuperscript{[10]} The symptoms are classified into muscarinic, nicotinic and central depending on the site of the compound over the respective receptors. Urination, lacrimation, emesis, miosis, excessive salivation, bradycardia, diarrhoea, and wheezing are the muscarinic features. Nicotinic features are paresis, fasciculation, tachycardia, and hypertension. Central features include confusion, anxiety, seizures, ataxia and psychosis.\textsuperscript{[11]} The clinical features are due to excess acetylcholine at the muscarinic and nicotinic receptors which leads to initial stimulation and eventual exhaustion of cholinergic synapses.\textsuperscript{[12]} Respiratory paralysis and cardiac arrest are considered as the most common causes of death in these patients. The myocardial damage is caused by both sympathetic and parasympathetic over activity.\textsuperscript{[13]} Yasue et.al.,\textsuperscript{[14]} discovered that parasympathetic over activity leads to coronary artery spasm, following that Horio et al\textsuperscript{[15]} injected acetylcholine into the coronary arteries and demonstrated coronary vasoconstriction. Kiss and Fazekas identified transient myocardial infarction in five patients among the 168 cases included in a study\textsuperscript{[16]}.

Diffuse myocardial damage was found at autopsy in two cases of malathion intoxication.\textsuperscript{[17]} Kathi et al conducted a study in 37 patients\textsuperscript{[18]} for a 3 year period of cardiac complication following organophosphorous intoxication; out of 37, 62.5\% that is 23 of 37 patients had cardiovascular injury, 29.7\% that is 11 out of 37 developed electrocardiographic changes suggestive of injury to myocardium (ST-T Changes); 3 out of 37 died, that is 8.1\%. CP Dalvi et al studied the correlation of electrocardiographic changes in organophosphorous poisoning with its prognosis. Wang Jian-dong studied the dynamic changes of cardiac enzymes and the acute poisoning with organophosphorous compounds.

Fasting serum level of troponin T and cardiac enzymes and its isoforms (Figure-1) (CK-MB, CK, AST, and LDH) in 92 patients with acute organophosphorous poisoning (AOPP) were measured following poisoning on 1,2,3,5 and 7 days, and measured one time in normal control group as well. There was an increase of different levels in troponin T and cardiac enzymes along with the degree of AOPP. They concluded that the level of cardiac troponin T and cardiac enzymes in patients with AOPP may be taken as a useful marker for the degree of poisoning and for prognosis. GUO Ya-ying et al\textsuperscript{[19]} studied the applied value of serum cardiac troponin T (cTnT) for diagnosing myocardial involvement in the acute organophosphorous poisoning. The serum cTnT and CK-MB were significantly higher than that in control group and increases with the degree of poisoning. They concluded that the level of serum cTnT increases significantly with the severity of AOPP and is a sensitive marker of myocardial injury.
The need of the hour is for newer biomarkers in relation to OP poisoning started a very long time ago. OP labelled albumin in plasma, blood beta-glucuronidase and paraxonase status were suggested by some scientists to be very reliable marker for both diagnosis of the poisoning and prognosis. But these assays are not available widely and are very costly. Many studies were conducted regarding this and were shown that Serum cholinesterase can be a useful tool in the diagnosis of OP poisoning. But its role in prognostication is very minimal. A number of recent studies were conducted using parameters like liver enzymes, serum amylase and serum CPK as newer markers and their correlation with severity and prognosis of OP poisoning.

**Figure 1:** Different Isoforms of creatine phosphokinase

### Pathology of Organophosphorous Compounds

The basic pathology is Ach binds with its receptors and releases calcium ions. In OPC poisoning due to excessive availability of Ach, which binds to its receptors, induces a mass inflow of calcium ions into cytosol, which leads to depolarization of muscle end-plates leading to muscular damage. The principal pharmacological action of all OPs is the inhibition of acetylcholinesterase; most patients die from cardio respiratory failure. However, there is much variation in the timing of onset and clinical features depending on the particular OP involved. OP poisoning has high inpatient mortality and many patients have cardio respiratory arrests after admission (38% of patients requiring intubation in one study). Cardiac complications are common and can be fatal if not diagnosed and treated early. The exact pathogenesis of cardiac complications has not yet been defined. A few important studies have been carried out both in India and abroad to study the cardiac complications and electrocardiographic (ECG) changes in OP poisoning. The current comprehensive study was reviewed out to understand the cardiac manifestations of OP poisoning with special reference to cardiac enzymes.

### Organophosphates Toxicity

Organophosphate toxicity is determined by several factors. Of these, the important ones are the route of contact, molecular structure, and its relation with the biotransformation and detoxification system in the body. Organophosphate compounds are absorbed through inhalation, ingestion, and also through integumentary system. The dissemination of Organophosphates is variable following absorption in the system. The complete classification and treatment of organophosphorous poisoning is depicted in Figure 2. The half-life of the compound is short in blood though in some cases it can be several days. OP compounds undergo extensive biotransformation in the body in various organs, by concurrent oxidative biotransformation at various points in the compound, using cytochrome P450 complex.

### Cardiovascular Disorders

Myocardial necrosis following Organophosphate poisoning was reported by Povoa et al[20]. Elevation in creatinine kinase and lactate dehydrogenase following organophosphate poisoning[21]. Sinus tachycardia, hypertension, sinus bradycardia, hypotension, impaired force of contraction, myocardial necrosis are the cardiac manifestations[22]. ECG changes are Prolonged QT interval, low amplitude T waves, ectopic beats, ST segment elevation, and PR interval prolongation[23].
Raised CPK-MB levels have been associated with acute OPC poisoning patients mainly due to skeletal muscle and respiratory muscle involvement. High levels of CPK-MB have been associated with mortality in acute OPC poisoning patients\textsuperscript{[24]}. The extent, frequency, and pathogenesis of the cardiac toxicity from these compounds have not been clearly defined. However, according to a recent report, the mortality rate has declined considerably following intensive management by using the POP scale (Table-1)\textsuperscript{[25]}. The current body of knowledge largely consists of limited studies and case reports. Therefore, many physicians may not be fully aware of the cardiac complications of OPC poisoning.

**Figure 2**: Classification and treatment of Organophosphorous poisoning
Table 1: Organophosphorous Poisoning (POP) Scale for grading the different parameters

| PARAMETER            | FINDINGS                        | SCALE |
|----------------------|---------------------------------|-------|
| Pupil Size           | ≥ 2mm                           | 0     |
|                      | < 2mm                           | 1     |
|                      | Pinpoint                        | 2     |
| Respiratory Rate     | < 20/Minute                     | 0     |
|                      | ≥ 20/minute                     | 1     |
|                      | ≥ 20/minute with cyanosis       | 2     |
| Heart Rate           | > 60/minute                     | 0     |
|                      | 41-60/minute                    | 1     |
|                      | < 40/minute                     | 2     |
| Fasciculation’s      | None                            | 0     |
|                      | Present, generalized.± continues| 1     |
|                      | Both Generalized & Continues    | 2     |
| Consciousness Levels | Conscious & Oriented            | 0     |
|                      | Impaired Verbal Response        | 1     |
|                      | No verbal Response              | 2     |
| Seizures             | Absent                          | 0     |
|                      | Present                         | 1     |

*Mild Poisoning-0-3, Moderate poisoning 4-7 and severe poisoning 8-11* [28]

Organophosphorous Compound Diagnosis

Organophosphate poisoning is usually diagnosed on the basis of clinical scenario. If known ingestion or exposure to OP agent is not evident, the clinical signs of cholinergic crisis may show the likelihood of organophosphate poisoning. Many organophosphate compounds have a characteristic garlic like or petroleum odour which is useful in making the diagnosis. Because of the significant variability in toxicity, effort must be made to precisely identify the agent involved. It is imperative to find out if a dimethyl or diethyl poison is involved. The duration of toxidrome and the therapeutic window during which the treatment with an oxime is likely to be effective are markedly different between these two groups of organophosphate compounds. Dimethyl compounds undergo rapid ageing, hence the therapy with oxime is critical; diethyl compounds exhibits delayed toxicity and hence require a prolonged treatment [27].

Clinical signs of Organophosphorus toxicity express when the cholinesterase values drop to less than 75%. It will be < 10% in clinically overt poisoning [28]. If there is a doubt whether an organophosphate is ingested or not, 1 mg of atropine in adults or 0.01 to 0.02 mg/kg of atropine in children can be tried. Following atropine injection if there is no signs and symptoms of anticholinergic effects then it suggests the diagnosis of poisoning with acetylcholinesterase inhibitor. Bardin’s classification is used for grading the patient according to clinical findings [29].

Abnormalities in Laboratory Parameters

Measurement of RBC cholinesterase activity is a measure of level of toxicity. Sequential measurement of cholinesterase levels also helps in assessment of adequacy of oxime therapy in regeneration of cholinesterase levels. Plasma cholinesterase estimation is easily done and hence employed in most of the laboratories but it does not correlate well with the severity of poisoning like RBC cholinesterase [30]. Several liver enzyme abnormalities are noted in OP poisoning including elevations in ALT, AST, and ALP. Serum amylase is also noted to get elevated because of excessive cholinergic stimulation of pancreas. Creatine phosphokinase get elevated in OP poisoning during the acute phase and also during the intermediate syndrome. Few studies have reported elevation in CPK-MB and troponin levels indicating myocardial necrosis in organophosphate poisoning.

Discussion

Organophosphorus (OP) pesticide poisoning is a major clinical and public health problem across the world including much of rural Asia [31]. It accounts for as much as 80% of pesticide-related
hospital admissions. Organophosphate compounds are widely used as insecticide in agriculture. For the reason that they are easily available, accessible and used widely, organophosphate toxicity is a significant universal health concern mainly in unindustrialized countries. Hundreds of thousands of deaths happen worldwide because of organophosphate agents.

Organophosphate ingestion is one of the supreme causes of suicidal deaths in India. The incidence of pesticide poisoning is very common among people of low socio economic status. It may be because of rapid urbanization, economic and social factors that contribute to depression and frustration in people. Those persons are the major victims of poisoning, when they are not able to cope up with these stressful situations. Hospitals in rural areas mainly handle the impact of this problem with a case fatality of 15–30%.

The possible mechanisms of cardiac toxicity are related to sympathetic and parasympathetic over-activity, hypoxemia, acidosis, electrolyte derangements and a direct toxic effect of the compounds on myocardium. On the other hand, the use of atropine as the antidote for OP poisoning itself may induce lethal arrhythmias. The lack of timely identification of the poisoning or its clinical toxidrome and failure to proper cardiac monitoring for potential life threatening complications may endanger the lives of the patients. Organophosphate poisoning by either intentional or accidental ingestion is still widely prevalent in developing countries and is responsible for roughly 200,000 (two-third of pesticide related Cholinergic) deaths year. The well-known presentations include:

1) Cholinergic crisis (overstimulation of muscarinic acetylcholine receptors) manifested by excessive salivation, lacrimation, diarrhea, and bronchorrhea;

2) Nicotinic excess (overstimulation of nicotine acetylcholine Neurological) causing tachycardia, mydriasis, hypertension, sweating;

3) Neurological (over stimulation of central nervous system muscarinic and nicotinic receptors) manifestations which can be acute (confusion, agitation, and coma), subacute (intermediate syndrome) or delayed (neuropathy due to chronic exposure).

The researchers revealed that CPKMB levels more than 40U/L have 10 to 20 times of odds of death within three days of admission. Compared to Dayanand et al study the mortality in patient with elevated creatine kinase was 39.47% as against 4.76% in patients with normal creatine kinase. Cardiac manifestations of organophosphate poisoning are often overlooked and an electrocardiography done at baseline may provide useful information to stratify severity of poisoning and plan further management. Association of poisoning with various arrhythmias including ventricular tachycardia been reported in literature. Cardiac complications have been noted in more than half of the patients in various case series, of which prolongation of QTc interval, ST-T changes were the common ones as our patient. Moreover hypotension and prolonged QTc interval have been described to be independent predictors of mortality. It has been shown by Senanayeke et al that the POP score can efficiently predict the severity, morbidity and mortality of OP poisoned patients and in our study we utilised the same scoring system and we found that majority of the patients had moderate to mild severity and only 24% of the patients had severe OPC poisoning.

Management of OP Poisoning

A rigorous organophosphate intoxication is a medical emergency. The management starts with patent airway, breathing, & circulation. O2 must be provided at the earliest. The victim is kept in left-lateral position along with extended neck. In order to keep the airway patent and reduce the risk of aspiration this position is useful. It also slows the gastric transit and hence decreases absorption of the poison. Stomach wash is effective if given within thirty minutes of poisoning, and if it
is delayed it can also be done on admission after confirming that the airway is secure. Induction of vomiting with emetics like ipecacuanha must be avoided, because unconsciousness can rapidly set-in before vomiting\textsuperscript{[42]}

In patients with topical exposure there is potential risk for dermal absorption and hence aggressive decontamination, complete removal of contaminated clothes from the body and complete cleansing of the involved parts must be done. Patients’ garments and stuffs that are contaminated must be cast-off because it can absorb the OP compounds and re-exposure to patient can occur even after washing. Health care workers should take necessary precautions to avoid accidental exposure to such contaminated clothing and also providing treatment in well ventilated areas\textsuperscript{[43]}. Moderate to severely intoxicated patients having depressed sensorium need 100% O\textsubscript{2} and endotracheal intubation for mechanical ventilation. Patients who appear to have mild poisoning may also quickly develop failure of respiration due to nicotinic receptor mediated diaphragmatic weakness, CNS respiratory center depression, bronchospasm and copious secretions. So these patients may also be considered for an early intubation. Patients with cholinergic toxicity due to organophosphate poisoning are treated with atropine and oxime therapy.

In one of the study the mean CPK is 802.38 IU/L and CPK MB is 191.76 IU/L Nermeeen AM et al\textsuperscript{[44]} have demonstrated increases in serum CPK and a proportionate fall in serum cholinesterase. The excess of acetylcholine in OP poisoning causes reversible muscle injury and rise in various muscle enzymes including CPK\textsuperscript{[45]} Dayanand Raddi et al\textsuperscript{[46]} conducted a study regarding CPK and OP poisoning and concluded escalation of CPK is evident of respiratory-failure and timely estimation of CPK has to be customarily taken as a prognostic indicator in OP poisoning. In acute OP poisoning many cardiac events like arrhythmias, non-cardiogenic pulmonary edema, hypertension, conduction defects, and ECG changes like transient ST elevation have been documented\textsuperscript{[47]}. The mechanism behind cardio toxicity of Organophosphates is not known. It is postulated that parasympathetic and sympathetic over activity causes myocardial damage. In a study conducted by Abbas Aghabiklooei et al\textsuperscript{[48]}, they have found out elevation of cardiac enzymes in acute OP poisoning and concluded myocardial involvement as a most significant cause of negative outcome in OP poisoning. They also hypothesized myocardial involvement as a good predictor of negative outcome in OP poisoning. Organophosphate poisoning had a higher level of markers of CK-MB, Troponin and CK-Total. Studies demonstrated that survived patients did not differ in duration of admission in hospital and estimated amount of ingested poison in comparison with survivors. To date, we are unaware of any study demonstrating higher serum levels of cardiac markers as a predictor of death in patients with organophosphate poisoning. There is a very few studies investigating the correlation between cardiac injury and intoxication. In a prospective study investigating the role of acute CO poisoning on cardiac injury suggested that it is not necessary to routinely measure CK, CK-MB and troponin-T in intoxicated patients. In the other hand some studies have suggested CO poisoning as a finding of myocardial damage in patients with CO poisoning seems to indicate an unfavorable long-term prognosis.

**Conclusion**

Organophosphorous compound can directly cause myocardial injury during the acute phase. Cardiac complications of OP poisoning can be life threatening and are not fully appreciated. The level of cardiac enzymes correlated well with the severity of poisoning and prognosis, suggesting its use as a prognostic indicator of OP poisoning. CPK-MB levels were frequently high among the OPC poisoning patients. On admission CPK-MB levels were significantly higher in patients with normal ECG as compared to abnormal ECG.
Mortality was observed in patients with QTc prolongation, VT and VF. Within each ECG parameter significant difference was observed in CPK-MB levels among survived and expired patients. Vigilant monitoring of the patients for prominent cardiac manifestations such as QT prolongation, VT or VF, and prompt treatment can save many patients. Serum CPK level can be used as an alternative biomarker in diagnosis or stratifying severity of acute OP poisoning, as it is cheap, easily available, especially in developing countries. The only disadvantage in using CPK levels as a predictor is that, the other causes of elevated CPK levels should be ruled out. The serum CPK levels in acute OP poisoning can also be used as a prognostic indicator for assessing the outcome measure. To substantiate our findings more number of multicentric studies with larger sample size has to be conducted. So, to conclude, serum CPK level can be an efficient biomarker in case of acute OP poisoning not only due to its easy availability and low cost, but also because serial monitoring of its level during the entire course of therapy can predict the prognosis. Serum creatine phosphokinase can be a simple, cheap and widely available biomarker for acute OP poisoning. It can be of particular importance in developing countries, where other costly biomarkers are difficult to estimate.

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