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An Analytical Study about Serum Creatine Phosphokinase as Predictor and Marker of Severity in Organophosphorus Poisoning

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Abstract

Introduction: Organophosphorus (OP) toxicity is an important global health problem, especially in many developing countries because of their widespread use and easy accessibility. The objectives of our study were to measure serial serum creatine phosphokinase (CPK) levels, to correlate CPK levels with severity of poisoning, and to record the total dose of atropine required. **Methods:** This was a retrospective and analytical study. One hundred patients of either sex, having age >14 years, presented within 12 h of ingestion or inhalation of OP. It was observed that confirmation of OP poisoning was done by seeing the packet/container with clinical presentation. Clinical severity was categorized according to Peradeniya organophosphorus poisoning (POP) scale. **Results:** The severity of the poisoning increased in respect to POP score, the serum CPK levels, and total dose of atropine required for treatment also increased. The difference in serial CPK levels in patients without intermediate syndrome (IMS) and with IMS, it was observed that the difference in CPK between these patients was highly significant at baseline and 48 h. There was an increase in CPK levels at admission and 48 h, but reduced by 96 h. A weak positive correlation was observed between POP score and CPK levels, as well as CPK, and atropine dose. A negative correlation was observed between butyrylcholinesterase and CPK levels. **Conclusion:** In our opinion, these observations suggest that there is a direct relation between serum CPK levels and IMS. Hence, it is necessary for estimating CPK levels, especially after 48 h, in moderate-to-severe poisoning patients so that IMS can be recognized at the earliest and patients can be referred to higher centers for immediate management of respiratory failure, reducing morbidity and mortality.

Keywords: Analysis, Creatine phosphokinase, Marker, Organophosphorus poisoning

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Introduction

Organophosphorus (OP) compound is one of the common causes of poisoning in rural India as they are easily available and visual OP toxicity is an important global health problem, especially in many developing countries because of their widespread use and easy accessibility.[1,2] Major toxic mechanism of OP compounds are irreversible inhibitors of carboxylic ester hydrolases, including acetylcholinesterase (AChE), erythrocyte cholinesterase (EChE), plasma or butyrylcholinesterase (BChE), and other nonspecific proteases. The primary toxicity from these compounds is derived from excessive stimulation of muscarinic and nicotinic cholinergic receptors by the accumulated acetylcholine in the central and autonomic nervous systems as well as at skeletal neuromuscular junctions.[3]

Various prognostic tools such as serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), serum immunoglobulins, and circulating complements for early detection of patients at high risk for developing respiratory failure have been tried.[3] There will be the elevation of serum CPK in OP poisoning due to myonecrosis caused by persistent depolarization at the neuromuscular junction and oxidative cellular damage to muscle membrane.[3,4] Serum CPK level has also been studied as a predictor for the onset of intermediate syndrome (IMS), but in earlier studies, CPK has been measured only at admission and/or before discharge.[3,4]

The objectives of our study were to measure serial serum CPK levels, to correlate CPK levels with severity of poisoning, and to record the total dose of atropine required.

Severity of Poisoning if identified early can reduce the need for ventilator support and the treatment can be initiated at the earliest. Hence, identifying the patients at high risk for IMS may lead to a decrease in morbidity and mortality.

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Methodology

After obtaining approval and written inform consent from patients, this retrospective, analytical study was conducted in 100 patients of either sex, having age >14 years, presented within 12 h of ingestion or inhalation and was admitted in the Department of Medicine in the local tertiary care hospitals in the past 1 year. The cases with indication of exposure to an entirely different poison other than OP poison, patients with OP poisoning and mixed with any other poison, chronic alcoholics patients, patients who had a history of chronic liver disease, myopathy, history of malignancy, renal disease, and history of intake of drugs such as – statins, fibrates, dexamethasone, aspirin, anticoagulants, and frusemide were excluded from the study.

This retrospective and analytical study involved prior permission / consent from Hospital Authorities & Medical

Superintendents of the randomly selected secondary & tertiary care local hospitals with the undertaking that data will be used only for study purpose. Medical record numbers were used to generate data for analysis.

The study was conducted within ethical standards and does not involve any direct intervention to any mentioned subjects nor any physical examination was performed. Randomization was done using computer tables in selecting data. All patients data had details of standard clinical examinations, routine biochemical and hematological investigations. For the purpose of the present study, data of 100 of the randomly selected patients (candidates/study subjects) were retrospectively identified. The medical records for these patients were reviewed for the collection and classification.

It was observed that confirmation of OP poisoning was done by seeing the packet/container with clinical presentation. Clinical severity was categorized according to Peradeniya organophosphorus poisoning (POP) scale[5] [Table 1].

It was observed that the levels of serum CPK, serum cholinesterase, and pH were measured following admission. CPK levels were estimated spectrophotometrically using the commercial kit of creatine kinase and using UV kinetic optimized method. Patients were treated according to standard treatment protocol of our hospital with atropine 3–5 ml (0.6 mg/ml) bolus followed by continuous infusion with titration based on clinical assessment, and pralidoxime 2 g bolus over 30 min followed by 1 g/h for 48 h. The total dose of atropine given to the patient till recovery was calculated. Data collected as per the pro forma included type of poison, time since poisoning, and POP score. Serial serum CPK levels were estimated at admission, 48 and 96 h after poisoning. Treating physicians were blinded to serial serum CPK values. Serum pseudocholinesterase or BChE was measured at admission.

Continuous data were expressed as mean ± standard deviation. The data were analyzed by IBM SPSS Statistics 23. All quantitative data were coded and transformed into an Excel master sheet for computer programming. A Chi-square test was used to evaluate categorical variables for analysis. Overall, $P < 0.05$ was proposed to represent statistical significance after correction.

Results

Data were collected from 100 study subjects/patients of which 67% were male and 33% females, with a mean age of 31.48 ± 11.76 years. The majority of them were laborers and farmers by occupation; others were students and housewives. Chlorpyriphos (28%) was the most common poison consumed followed by triazophos and methyl parathion each and rest were combinations. The average time was taken to reach the hospital which was 204.86 ± 47.53 min.

We observed that as the severity of the poisoning increased in respect to POP score, the serum CPK levels and total dose of atropine required for treatment also increased. The levels of BChE were reduced. Shapiro–Wilk normality test was applied for CPK distribution, it was not Gaussian distribution, probably the five patients with had a mean CPK (IU/L) of 1827.33 ± 223.29, and in others, it was 219.51 ± 136.21.

The difference in serial CPK levels in patients without IMS and with IMS, it was observed that the difference in CPK between these patients was highly significant at baseline and 48 h.

In analysis, five patients with moderate poisoning developed IMS. CPK levels at 48 h in these patients were 2010 IU/L, 1972 IU/L, and 1832 IU/L, which is much higher than CPK levels in the patients without IMS. Among them, four patients needed mechanical ventilation. The fifth patient developed tachypnea, weakness, and fall in $SPO_{2,}$ so the patient was under observation in ICU for 24 h. All these patients recovered completely.

Figure 1 depicts the serial serum CPK levels, there was an increase in CPK levels at admission and 48 h, but reduced by 96 h. A weak positive correlation was observed between POP score and CPK levels, as well as CPK, and atropine dose. A negative correlation was observed between BChE and CPK levels [Table 2].

Discussion

OP compounds are the most commonly used pesticides in agriculture. Because of their wide use and easy accessibility, poisoning with these compounds has emerged as an important health problem, especially in developing countries. Acute OP poisoning can manifest with three different phases of toxicity namely acute cholinergic crisis, IMS, and OPIDN. Inhibition of AChE is the major mechanism of cholinergic crisis, which leads to stimulation of muscarinic and nicotinic receptors. Muscarinic features include excessive salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, emesis, blurred vision, miosis, bradycardia, and wheezing. Nicotinic features include fasciculation, paresis, or paralysis. Central receptor features include anxiety, confusion, psychosis, seizures, and ataxia.[6]

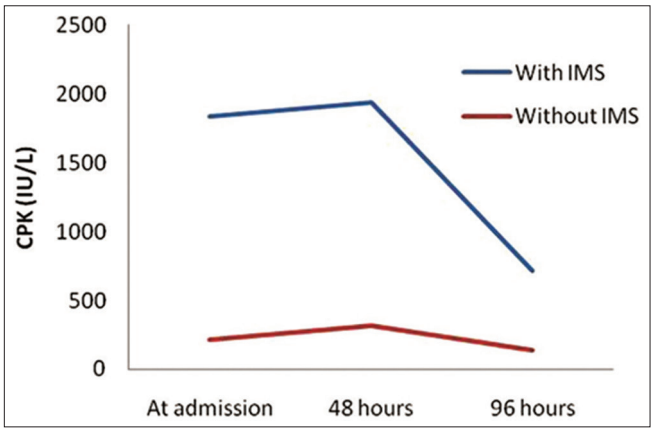

Figure 1: Serial serum creatine phosphokinase levels

Table 1: POP scale

POP score	*Severity*	*Number*	*Percentage*
0–3	Mild	43	43
4–7	Moderate	36	36
8–11	Severe	21	21

POP: Peradeniya organophosphorus poisoning

Table 2: Correlation between and atropine dose and POP, CPK, and BChE

Parameters	*Pearson's coefficient (r)*	*P*
CKP versus POP	0.368	0.0012
CKP versus BChE	0.31	0.023
CKP versus atropine dose	0.418	0.001

BChE: Butyrylcholinesterase, POP: Peradeniya organophosphorus poisoning, CPK: Creatine phosphokinase

Studies have shown that IMS occurred between 48 h and 96 h after acute poisoning and is characterized by weakness of proximal limb muscles, neck flexors, respiratory muscles, and is attributed to muscle fiber necrosis. Reversible myocyte injury results in increased muscle enzymes such as myoglobin, LDH, troponin, and CPK. Serum CPK rises in 6 h following muscle injury and remains elevated for 5–6 days.[7]

Patients in our study were mostly in the third decade who would contribute to the economic status of the family. Various reasons contributing for consumption of poison were a financial loss, family disputes, and stress. Chlorpyriphos was most commonly consumed as it is the widely used pesticide in this area. There was a delay in patient reaching the hospital, which could be attributed to lack of transport facility in rural areas.

Mild and moderate OP poisoning patients had elevated serum CPK level at least in one of the three serial measurements. These findings were similar to other studies where they have tried to develop serum CPK as a tool for diagnosing the severity of OP poisoning and also as a prognostic marker for the recovery from OP poisoning.[8] Another study has shown raised serum CPK level only in a fraction of their patients who had severe poisoning.[9]

We have observed that three patients with IMS had marked elevation of CPK at baseline and 48 h and required intensive care. Similar findings were observed in other studies, where the serum CPK levels were more than 10,000 IU/L in moderate-to-severe poisoning, and they had recovered completely.[8] In our study, a weak positive correlation was observed between serum CPK levels, POP score, and dose of atropine, but another study has shown a strong positive correlation.[8]

Conclusion

These observations suggest that there is a direct relation between serum CPK levels and IMS. Hence, it is necessary for estimating CPK levels, especially after 48 h, in moderate-to-severe poisoning patients so that IMS can be recognized at the earliest and patients can be referred to higher centers for immediate management of respiratory failure, reducing morbidity and mortality.

Study limitations

The main limitations of this study include its retrospective design (data of past admitted patients) with a limited number of participants (n = 100). We have not studied the long-term outcomes, and it may be that although we are not seeing any difference in short-term outcomes, they may become apparent in the long term.

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