ORIGINAL ARTICLE

Relevance of Plasma Cholinesterase to Clinical Findings in Acute Organophosphorous Poisoning

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Introduction: Organophosphorus (OP) poisoning is a major public health problem in developing world. OP pesticides inhibit carboxylic esterase enzymes including plasma cholinesterase (PChE). Clinical manifestations following OP poisoning can be associated with the extent of decrease of PChE. This study was designed to investigate the relevance of PChE level to clinical manifestations in OP poisoning and to evaluate usefulness of PChE in predicting clinical outcomes.
Methods: This was a cross-sectional study which was conducted at Jawaharlal Nehru Medical College, Karnataka from 1st October 2009 to 30th September 2010. Seventy-six OP poisoned patients were enrolled and their clinical manifestations were recorded. 5-ml samples of intravenous blood were collected from each patient (on first day and fifth day of treatment) under strict aseptic precaution and the PChE level was measured.
Results: In total, mean age of patients were 25.5 (range: 21-30) years. Majority of patients were males (65.7 %), from rural areas (86.84 %) and agricultural workers (25%). Main clinical findings at the time of admission were congested conjunctiva (87%), pin point pupil (83%), lacrimation (80%), vomiting (78%), non-reactive pupil (75%), respiratory distress (60%) and abdominal pain (37%). Mean (SD) PChE at 6 hours post-exposure was 3672.4 (4200.1) IU/L. At presentation, cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation were related to cases with >75%reduction of PChE, while, constricted and non-reactive pupil, lacrimation and congested conjunctivae were related to cases with 50-75% reduction and abdominal pain, dryness of conjunctiva, vomiting and diarrhea were related to <50% reduction. Deceased cases had the lowest mean PChE level at presentation (1270.2). Death was mostly observed among patients who had respiratory distress.
Conclusion: A relative relationship between PChE level and clinical manifestations and outcomes was found. These findings can assist health professionals to better evaluate patient's prognosis and improve their treatment plan.

Keywords: Organophosphorous compounds; Acute poisoning; Acetyl Cholinesterase; Pesticide

INTRODUCTION

Pesticide poisoning is a major public health problem in developing world (1). Millions of people are exposed to danger of hazardous occupational practices and unsafe storage of pesticides (2). However, it is deliberate self-poisoning which causes the great majority of deaths and places immense strain on hospital services, particularly in Asia (3,4). According to a World Health Organization report, three million cases of pesticide poisoning occur annually worldwide and most of them are in Asia which at least half of them are due to organophosphorus (OP) poisoning (5).

Poisoning is a common method of suicide, especially in the developing world (6). OP compounds are amongst the most common poisons used for deliberate self-poisoning in India and other parts of the world (7-12). The exact rate of OP poisoning in India is uncertain due to lack of data and proper reporting. In many reports from India, rate of suicidal poisoning with OP compounds ranges from 10.3to 43.8% (8,13,14). Among OP poisoned patients in India, hospital mortality rate is reported to be as high as 20-70% (15,16). However, in United Kingdom, OP compounds are responsible for only about 1% of deaths. This is because in developing countries, facilities are limited for early diagnosis and treatment.

Being predominantly an agricultural country, OP compounds are used abundantly for farming in India. Hence, access to these hazardous chemical substances is easy. OP pesticides inhibit carboxylic esterase enzymes including acetylcholinesterase (AChE) and plasma cholinesterase (PChE). AChE can be found in erythrocytes, nervous tissue and skeletal muscles, while PChE can be found in plasma, liver, heart, pancreas and brain. Most of clinical manifestations associated with exposure to OP compounds have been attributed to inhibition of these enzymes (17).

Although it has not been fully studied, these anti-cholinesterase effects can be associated with the extent of decrease of AChE and PChE. This study was designed to investigate the relevance of PChE to clinical manifestations following OP poisoning and to evaluate usefulness of PChE in predicting clinical outcomes.

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METHODS

This was a prospective cross-sectional study which was conducted at Dr. Prabhakar Kore Hospital and Medical Research Centre, Jawaharlal Nehru Medical College, Belgaum, Karnataka from 1st October 2009 to 30th September 2010 after taking approval from the ethical committee. 76 patients with definitive diagnosis of OP poisoning were enrolled. Exclusion criteria were liver dysfunction, malnutrition, chronic infections, hypersensitivity reaction, pregnancy, age of more than 60 years and being on some specific medications including succinyl choline, codeine and morphine.

Each patient was assessed according to severity of OP poisoning based on Proudfoot classification (Table 1) (18). Patients who had manifestations suggestive of severe poisoning were assessed and ventilatory support was administered for them if they had any of the following signs: 1) Apnea 2) Obvious hypoventilation 3) Persistent cyanosis in spite of O2 supplementation 4) Persistent tachypnea or respiratory rate >24/minute 5) Persistent SpO2 <90% with oxygen supplementation 6) Active involvement of accessory muscles of respiration.

Four 5-mL samples of intravenous blood were collected from each patient under strict aseptic precautions on first day. Also, a fifth blood sample was collected and analyzed for PChE level on the fifth day of treatment. This time (day 5th on treatment) was selected as it has been considered to be the average time required for effect of pralidoxime to eliminate respiratory distress and need for mechanical ventilation (19). The PChE level was measured using Dimension Clinical Chemistry System (E.I. Dupont De Nemours & Company Inc., Wilmington, DE, USA). The normal values of PChE range from 5100 to 11700 with mean (SD) of 8440 (1780) IU/L (20,21). Based on Proudfoot classification, mild OP toxicity is defined as less than 10% reduction of PChE, moderate toxicity as 10-50% reduction and severe toxicity as >50% of reduction. In keeping with this definition, 4590-5100 IU/L PChE can be considered as mild, 2550-4590 IU/L as moderate and less than 2550 IU/L as severe toxicity.

Data are shown with frequency and percentage. Mean and standard deviation (SD) were calculated using Statistical Package of Social Sciences (SPSS Inc., Chicago, IL, USA).

RESULTS

Socio-demographic

In this study, 76 patients were enrolled with mean age of 25.5 (range: 21-30) years. Majority of patients were males (n=50, 65.7 %), were from rural areas (n=66, 86.84 %) and were agricultural workers (n=19, 25%) who consumed OP compounds orally with the intension of self-poisoning. Monocrotophos, a highly hazardous OP compound, was the most common used poison among the patients (60%) which could be due to frequent use and easy availability in our state, Karnataka.

Clinical and Laboratory Findings

Main clinical findings at the time of admission were congested conjunctiva (87%), pin point pupil (83%), lacrimation (80%), vomiting (78%), non-reactive pupil (75%), respiratory distress (60%) and abdominal pain (37%). Among 46 patients with respiratory distress, 35 patients required ventilatory support. The average time taken for initiating active weaning was 4.3 days post-admission in

Table 1. Assessment of Severity of Acute Organ phosphorous Compound Poisoning

	SEVERITY		
	Mild	Moderate	Severe
Clinical Manifestations	Fatigue, Headache, Paresthesia, Nausea and Vomiting, Diaphoresis, Salivation, Abdominal pain, Diarrhea, Able to ambulate	Symptoms of mild poisoning + Miosis, General weakness, Dysarthria, Fasciculation, Unable to ambulate	Generalized Fasciculation, Marked miosis (Absent pupillary reaction), Flaccid Paralysis, Pulmonary crepitation, Respiratory distress, Cyanosis, Unconsciousness
Plasma Cholinesterase level	< 10 %	10-20 %	< 50 %

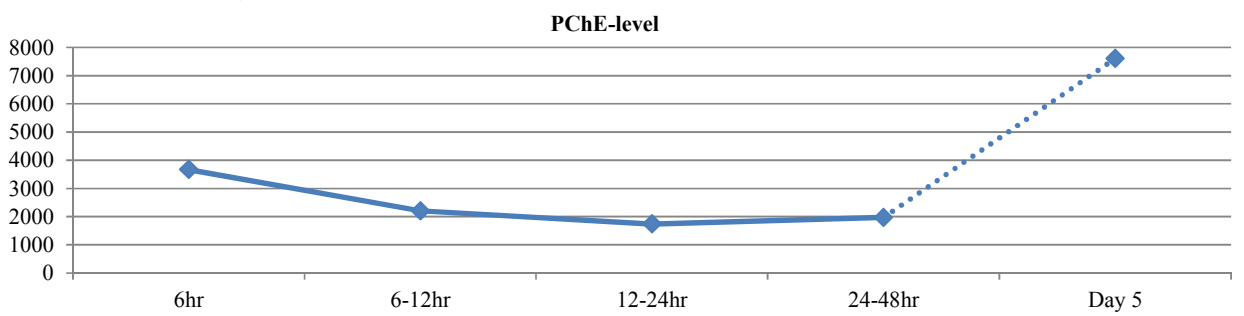

Figure 1. Mean Plasma cholinesterase levels in patients with organ phosphorous poisoning in different times of sampling post-admission.

the Intensive Care Unit. After an average of 7.4 days, patients were successfully weaned off from ventilator.

Mean (SD) PChE at 6 hours post-exposure was 3672.4 (4200.1) IU/L. PChE level then decreased to 2205.7 (2565.2) at 6 to 12 hours post-exposure and 1739.1 (1583.8) at 12 to 24 hours post-exposure. At 24 to 48 hours post-exposure mean PChE started to rise to 1966.4 (2525.8). After 5 days of treatment, PChE level reached a mean of 8587.7 (4728.3) (Figure 1). At presentation, 62 patients (90%) had PChE values of less than 5000 IU/L. In addition, in over 50% of patients, PChE suppressed to less than 2000 IU/L (severe toxicity).

Relevance of Plasma Cholinesterase to Clinical Manifestations

To assess the relationship of clinical manifestations with levels of PChE, mean PChE level for each manifestation was measured independently at the time of presentation. As it is shown in figure 2, cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation were related to cases with very severe suppression of PChE (>75%). In this respect, cyanosis was noted in 5 cases and was related to the lowest mean PChE level (847.2 IU/L). In association with less than 50% PChE reduction, abdominal pain, dryness of conjunctiva, vomiting and diarrhea were found. For PChE levels of 50 to 75% of normal, pin point and non-reactive pupil, lacrimation and congested conjunctivae were noted.

Relevance of Plasma Cholinesterase to Morbidity and Mortality

Mean PChE was further measured according to some important complications following OP poisoning (Table 2). Patients who died had the lowest mean PChE level on first day (1270.2). Among survived patients, those who required ventilatory support had the lowest PChE (1383.7) on first day. Subsequently, in the cases presented with muscle weakness, convulsion, respiratory distress and fasciculation, mean PChE on first day was very low as it was reduced to 1739.1, 1899.5, 1966.4 and 2205.7 respectively (severe toxicity). In addition, patients with muscle weakness and

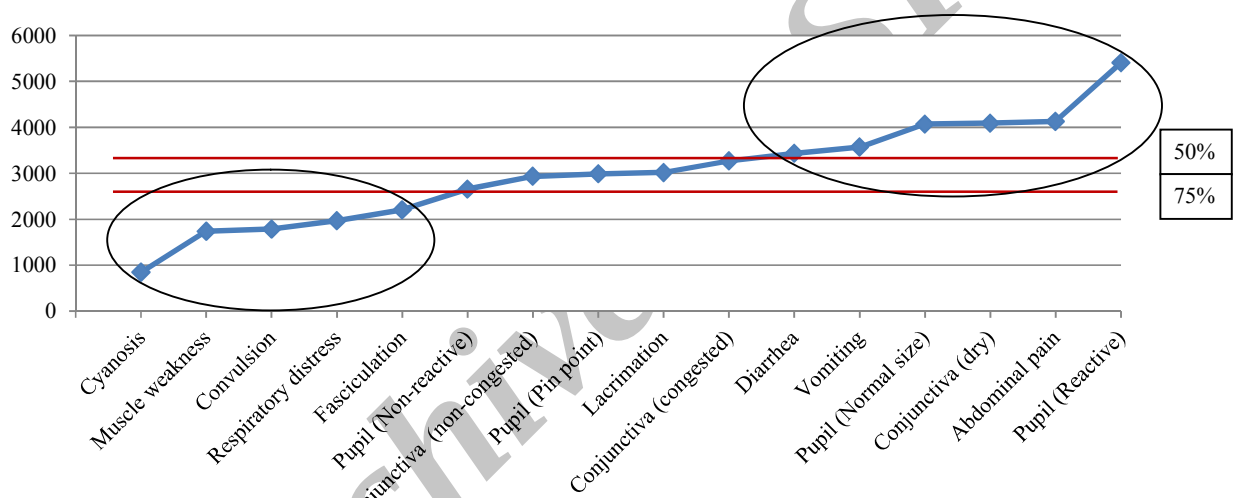

Figure 2. Level of plasma cholinesterase in association with clinical manifestations

Table 2. Comparative data of morbidity and mortality

Features	No. of Patients	Oxygen saturation-Day 1 (SpO2), mean (SD)	PChE-Day 1 (IU/L), mean (SD)	PChE-Day 5 (IU/L), mean (SD)
Oxygen therapy with mask	16	80.6 (15.2)	5605.5 (5234.6)	10346.5 (4089.9)
Respiratory distress	46	69.5 (17.9)	1966.4 (2525.8)	7356.6 (4228.3)
Ventilatory support	35	67.7 (17.9)	1383.7 (1232.5)	6636.5 (4277.3)
Fasciculation	17	70.0 (19.3)	2205.7 (2565.2)	6369.4 (5417.6)
Muscle weakness	7	67.8 (22.3)	1739.1 (1583.8)	6164.2 (3500.9)
Convulsion	6	79.5 (14)	1899.5 (1353.8)	7053.4 (2162.2)
Survived	62	80.6 (18.8)	3672.4 (4200.1)	8587.7 (4728.3)
Died	14	70.3 (16.8)	1270.2 (1456.2)	9459.4 (7656.0)*

* 9 patients died within 5 days and 5 others thereafter.

fasciculation had the lowest blood oxygen saturation (SpO2<70%) on first day, indicating severe respiratory distress (Table 2). Death was mostly observed among patients who had respiratory distress. Overall mortality was within the first two days.

DISCUSSION

OP poisoning is a major health problem worldwide, especially in developing countries with millions of victims and deaths occurring each year. Determination of AChE and PChE level in blood has remained as a mainstay for the fast initial screening of acute OP exposure which helps health-care professionals to establish early diagnosis and immediate treatment plan (22). However, it has been believed that these tests lack sensitivity and specificity, and additionally they might not be related to severity of poisoning (19,22). In this respect, Aygun et al. showed that PChE level is useful in diagnosis of OP poisoning in acute phase but it is not correlated to severity of poisoning and also morbidity and mortality (23). Conversely, Goswamy et al. demonstrated that apart from clinical indicators, low PChE levels were of greatest predictive value in OP poisoning (24).

In this study, we found that cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation were linked to very low PChE levels. Moreover, we found that as PChE level falls, the O2 saturation decreases and leads to respiratory distress which was the main cause of death among patients. This can be explained by the fact that mitochondria are the target of OP compounds (25). Therefore, a more severe OP poisoning which shows itself with lower PChE levels is associated with cellular hypoxia and subsequently severer life-threatening manifestations.

Similar to our findings, Kar in 2006 and Tsao et al. in 1990 showed that fatal outcomes following OP poisoning were associated with lower PChE levels (26,27). In addition, they found that all deceased patients had respiratory failure. In this regard, it has been ascertained that the essential cause of death in OP poisoning is respiratory failure which is due to weakness of the respiratory muscles, paralysis of the respiratory centre, bronchospasm and increased bronchial secretion (28). Furthermore, it has been proposed to consider miosis and muscle fasciculation for the control of treatment in OP poisoning (28).

In the present study, we found that deceased patients had the lowest PChE level at presentation. Likewise, Chen et al. showed that low PChE activity with non-rising trend within 48 hours of OP poisoning was associated with higher mortality (29). Moreover, Eddleston et al. revealed that PChE activity can predict death based on the formula of OP compound ingested (30).

LIMITATIONS

Although in this study we tried to identify the relevance of mean PChE level with each clinical manifestation, overlapping of features were present in some cases which can reduce the value of our findings. Therefore, to clarify the controversies, further studies with larger samples are recommended while the amount of OP compound consumed is strictly noted. Furthermore, Eddleston et al. proposed that predicting death with PChE level is possible when the ingested OP compound is known (30). However, in this study, we did not separate the results and outcomes based on the OP poison formula.

CONCLUSION

A relative relationship between PChE level and clinical manifestations and outcomes was found. These findings can assist health professionals to better evaluate patient's prognosis and improve their treatment plan.

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