ORIGINAL ARTICLE

Reduced Levels of Serum Potassium and Plasma Cholinesterase in Acute Organophosphate Poisoning: Possible Predictive Markers

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Abstract

Background: It is becoming apparent that although inhibition of cholinesterase plays a key role in organophosphate (OP) toxicity, other factors are also important. One of the contributing factors for severity of OP poisoning is electrolyte imbalances such as hypokalemia. This study was aimed at evaluating the value of hypokalemia in association with plasma cholinesterase (PChE) levels in predicting morbidity and mortality of acute OP poisoning.
Methods: In this cross sectional study patients with definitive diagnosis of OP poisoning were enrolled. Pre-interventional clinical features were observed and noted with severity assessment as per Proudfoot classification, along with measurement of serum potassium ion ([K+]) concentration and PChE level.
Results: Fifty OP poisoned patients (33 men, 17 women) were enrolled with median age of 27.1 years. The most common clinical manifestation was congested conjunctiva (82%) followed by miosis (78%) and bronchorrhea (78%). A total of 21 cases presented with one or more severe clinical features according to Proudfoot classification. Among them, 61.9% of cases (13 out of 21) developed hypokalemia. Muscle weakness or fasciculation developed with mean serum [K+] of 3.31 ± 0.11. Ventilatory support was required at the mean serum [K+] of 3.27 ± 0.10 mmol/L. Fatality was noted when the mean serum [K+] reduced to 2.90 ± 0.06 mmol/L. Correlation of the clinical effects and serum [K+] was significant ($P < 0.001$). In addition, muscle weakness, fasciculation, convulsion and respiratory distress were associated with marked suppression of PChE (>75%). Death was mostly observed among patients who had respiratory distress associated with hypokalemia and grossly reduced PChE.
Conclusion: For severe clinical features of OP poisoning, serum [K+] and PChE level are greatly reduced. Hence, these biochemical findings can be proposed as OP poisoning predictive markers. Clinicians and medical toxicologists should consider hypokalemia associated with reduced PChE level as alarming signs of poor prognosis in OP poisoned patients.

Keywords: Butyrylcholinesterase; Hypokalemia; Organophosphate Poisoning; Prognosis

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INTRODUCTION

India is the largest producer of pesticides in Asia and ranks twelfth in the world with regards to pesticide use, with an annual production of 90,000 tons (1). Organophosphate (OP) compounds are the most common agents consumed for poisoning in India due to their easy availability (1). Moreover, millions of Indian people are exposed to danger of hazardous occupational practices (2). Deliberate self-poisoning with pesticides, especially OP compounds, is an important public health problem worldwide that kills an estimated 200,000 people annually and its incidence keeps rising (2).

OP compounds act by inhibiting acetyl cholinesterase at muscarinic and nicotinic receptors. Hence, erythrocyte cholinesterase and plasma cholinesterase (PChE) reduce in OP poisoning (3); however, the value of measurement of these enzymes for assessment of the prognosis of patients is yet controversial. Any reduction in PChE level usually clinches the diagnosis of acute OP poisoning (4). Hence, this biochemical marker has been used for the diagnosis of acute OP poisoning cases as well as for better evaluation of patients and adjusting the treatment plan (5). Determination of PChE activity in blood has remained a mainstay for the fast initial screening and establishment of early diagnosis so that proper and immediate intervention could be possible (6). Despite remarkable progress in understanding the mechanisms of OP toxicity as the result of cholinesterase inhibition, the precise health effects following exposure to OPs are yet to be completely defined. The inhibition of cholinesterase per se cannot account for the wide range of OP effects. It is becoming apparent that although inhibition of cholinesterase plays a key role in the toxicity of OP compounds, individual susceptibility, inhibition of other enzyme systems and the direct effects of OPs on tissues are also important (7). One of the contributing factors for severity of OP poisoning is electrolyte imbalances. In acute OP poisoning, the most frequent cause of mortality is respiratory arrest and acidosis as the result of respiratory muscle paralysis (8). Hypokalemia is also a frequent finding

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in OP poisoning. Associated hypokalemia reinforces the muscle weakness. Hence, hypokalemia can be considered as an important factor for intensifying the poisoning.

This study was aimed at evaluating the value of hypokalemia in association with PChE level in predicting morbidity and mortality of acute OP poisoning.

METHODS

Following ethical clearance, a cross-sectional study 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. Patients with definitive diagnosis of OP poisoning were enrolled in the study, while cases with previous history of liver dysfunction, malnutrition, chronic infections, hypersensitivity reactions, pregnancy, age of over 60 years and being on some specific medications including succinyl choline, codeine and morphine were excluded. Pre-interventional clinical features were observed and noted with severity assessment as per Proudfoot classification (9), along with measurement of serum potassium ion ([K+]) concentration and PChE level. The serum [K+] levels of less than 3.5 mmol/L were considered as hypokalemia. 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 (10, 11). Data are presented with median or mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Using Statistical Package of Social Sciences (SPSS Inc., Chicago, IL, USA), the data were analyzed. One-way ANOVA test was used to compare the means of serum [K+] between different clinical features.

RESULTS

Demographic features

In this study 50 OP poisoned patients (33 men, 17 women) were enrolled with median age of 27.1 years. According to intention of poisoning 42 cases (84%) were suicidal, 7 cases (14%) were accidental and 1 case (2%) was due to occupational exposure. Monocrotophos was the commonest type (62%) of OP compound consumed.

Baseline clinical features

Clinical manifestations of the patients are summarized in table 1. The most common clinical manifestation was congested conjunctiva (82%) followed by miosis (78%), bronchospasm/bronchorrhea (78%) and vomiting (74%). A total of 21 cases presented with one or more severe clinical features according to Proudfoot classification (Table 2).

Serum potassium alterations in severe cases

Among severe cases, 61.9% (13 out of 21) developed hypokalemia. Among all patients, 34% (17 cases) had muscle weakness or fasciculation with mean serum [K+] of 3.31 ± 0.11, showing that as the serum [K+] level decreases below 3.5 mmol/L, these alarming signs can be recognized. The development of muscle weakness or fasciculation was in association with steady decrease in oxygen saturation level. This gradually progressed to respiratory distress to such a level that ventilatory support was required at the mean serum [K+] of 3.27 ± 0.10 mmol/L. Fatality was noted when the mean serum [K+] reduced to 2.90 ± 0.06 mmol/L. For these conditions, the correlation of the clinical effects and serum [K+] was significant ($P < 0.001$).

Table 1. Clinical manifestations of OP poisoned patients (n = 50)

Clinical manifestations	No. (%)
Bronchospasm/broncorrhea	39 (78)
Vomiting	37 (74)
Respiratory distress	24 (48)
Abdmoinal pain	15 (30
Sialorrhea	13 (26)
Fasciculation	12 (24)
Muscle weakness	5 (10)
Convulsion	4 (8)
Diarrhea	3 (6)
Lacrimation	2 (4)
Cyanosis	2 (4)
Conjunctiva	
Congestion	41 (82)
Watery	37 (74)
Pupil	
Miosis	39 (78)
Mydriasis	8 (16)

Plasma cholinesterase alterations in severe cases

Among the severe cases, the PChE level was remarkably reduced except in two cases (Table 2). The relevance of PChE to clinical manifestations was assessed independently at the time of presentation. As it is shown in table 3, muscle weakness, fasciculation, convulsion and respiratory distress were associated with marked suppression of PChE (>75%). For these clinical effects, considerable reduction in serum [K+] was also evident (Table 3). Mean PChE was further measured according to fatality following OP poisoning. Patients who died had the lowest mean PChE level (464 IU/L) with marked hypokalemia (2.9 mmol/L). Among the survivors, those who required ventilatory support had the lowest PChE levels (1383.7 IU/L). Death was mostly observed among patients who had respiratory distress associated with hypokalemia and grossly reduced PChE (Table 2). Overall mortality was within the first two days. There was a generalized decrease in PChE and serum [K+] levels from day one of poisoning to subsequent days in association with morbidity and mortality without any fixed trend. The relevance of severe clinical manifestations with PChE and serum [K+] levels is shown in figure 1.

DISCUSSION

Toxicity of OPs occurs when these compounds bind to acetylcholinesterase (AChE), preventing hydrolysis of acetylcholine and resulting in its accumulation in the

Table 2. Plasma cholinesterase and serum potassium levels in patients with severe organophosphate poisoning

Patient's Serial No.	$[K^+]$ (mmol/L)	PChE (IU/L)	Muscle weakness or fasciculation	Respiratory distress	Convulsion	Mortality
6	3.4	5243	-	-	-	-
8	2.8	640	+	+	-	+
10	4.0	2652	-	-	+	-
13	3.4	424	+	+	-	-
16	3.1	1073	+	+	-	-
18	3.0	220	+	+	-	+
19	3.8	461	+	+	-	-
20	2.8	1034	+	+	-	-
21	3.5	7799	+	-	-	-
22	2.8	231	+	+	-	+
24	3.9	1690	+	+	-	-
25	3.3	3141	+	+	-	-
27	4.6	855	+	-	-	-
35	3.6	1490	+	+	+	-
37	3.8	2015	-	+	-	-
39	3.0	765	+	-	-	+
40	3.3	1520	+	+	-	-
41	3.0	11615	+	+	-	-
46	3.9	1515	-	-	+	-
47	3.3	14488	+	+	-	-
50	3.2	2000	+	-	-	-
Total	3.40 ± 0.47	2898.61 ± 3845.53	17 (80.9%)	14 (66.6%)	3 (14.3%)	4 (19.0%)

PChE (IU/L): Plasma cholinesterase [K+]: Serum potassium +: Present -: Absent

Table 3. Mean plasma cholinesterase and serum potassium levels in association with severe clinical features in organophosphate poisoned patients

Clinical Features	Mean $[K^+]$ (mmol/L)	Mean PChE (IU/L)	Mean PChE (IU/L) with hypokalemia
Convulsion (no hypokalemia was seen)	3.83	1885.66	---
Muscle weakness or fasciculation	3.31	2908.58	3095.91
Respiratory distress	3.27	2860.14	3438.60
Mortality	2.90	464.00	464.00

PChE (IU/L): Plasma cholinesterase [K+]: Serum potassium

synaptic cleft. Balali-Mood revealed that hypokalemia may aggravate muscular weakness due to inhibition of AChE by OP compounds (12). We also found that remarkable reduction in serum [K+] is related to OP toxicity induced muscle weakness, paralysis and ultimately death. These findings may suggest that alteration in serum [K+] may alter neuro-muscular junction activity and contribute to overall morbidity and mortality of OP poisoning. The patients in the present study developed grievous signs and symptoms sequentially as the [K+] reduced. The decrease in [K+] was directly proportional to the onset of severe signs and symptoms.

Potassium ion is tightly balanced that urinary potassium excretion (1-1.5 mmol/Kg/day) is directly proportional to the total body potassium and is a good marker of total body potassium (13). The resting membrane potential and functional activity of electrically excitable cells undergo significant alteration even due to minute changes in extra-cellular potassium concentration (13). In acute cases of OP poisoning, due to strong nicotinic actions, respiratory distress, muscle weakness and paralysis sets in. In such stressful conditions, hypokalemia can be established as an add-on to the clinical burden and/or these signs and symptoms can be aggravated in the presence of associated

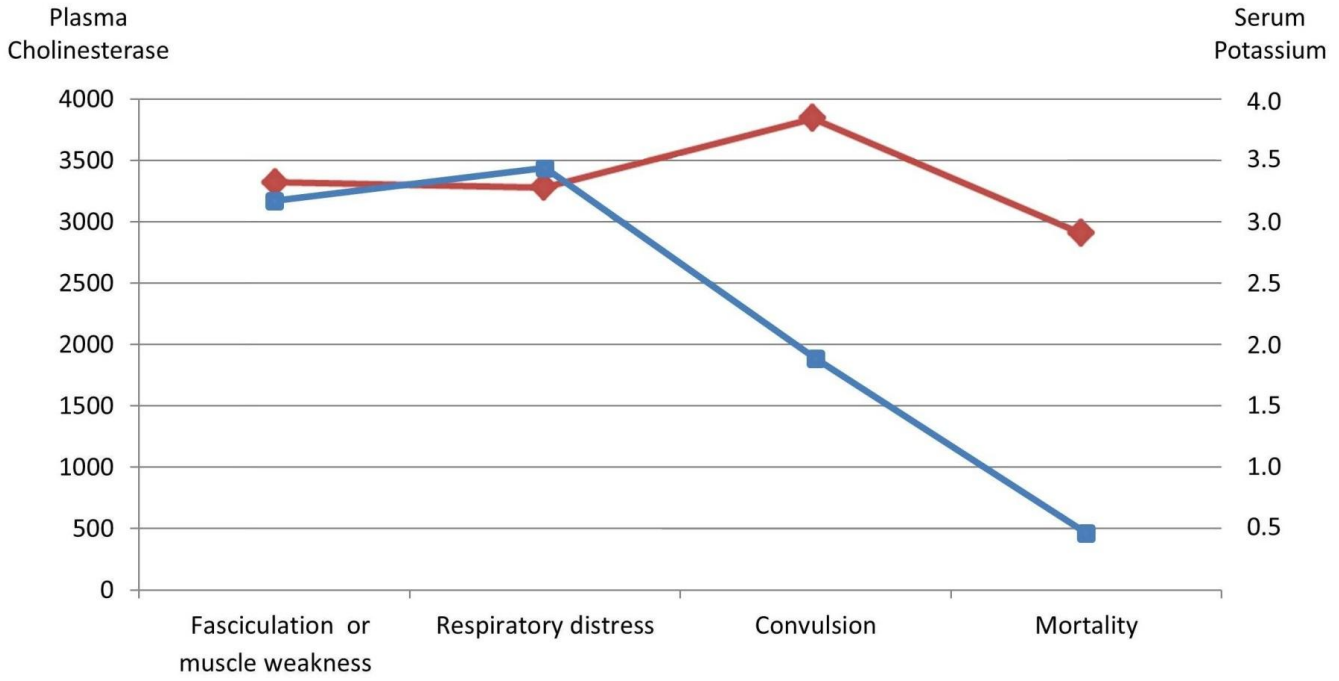

Figure1. The mean plasma cholinesterase and serum potassium levels in association with severe clinical features. The blue squares show the levels of plasma cholinesterase and the red squares show the levels of serum potassium.

hypokalemia. Hypokalemia manifests with lassitude, muscular weakness, and loss of deep tendon reflexes, paralysis, and death (which is usually due to cardiac arrhythmias and respiratory distress) (13). Cause of death in both acute OP poisoning and hypokalemia is usually muscular weakness and respiratory distress. It is not uncommon for patients with severe weakness to have a markedly low serum [K+] (14). Hypokalemia and paralysis are potentially reversible medical emergencies (15), however, when these features were coupled with reduction of PChE, higher chance of morbidity and mortality was observed (Figure 1). Hence, the level of PChE and serum [K+] can be proposed as OP poisoning predictive markers.

Hypokalemia induced morbidity and mortality are related to complications secondary to cardiac arrhythmia or respiratory failure (13). Although there are many potential causes for hypokalemia, there are far fewer entities in the differential diagnoses of hypokalemia and paralysis (15). Except OP poisoning, hypokalemic periodic paralysis which occur in autosomal dominant channelopathy characterized by muscle weakness or paralysis with a matching fall in serum [K+] levels (primarily due to defect in a voltage-gated calcium channel) is another etiology for concomitant presence of hypokalemia and paralysis (16-18). The differential diagnoses in a patient with hypokalemia and paralysis can be challenging. Nevertheless, it is important to make the diagnosis promptly because different therapies are required for each cause.

CONCLUSION

Given the high prevalence of OP poisoning and limited facilities for diagnosis and treatment of its sudden grievous clinical features, this health problem will continue to be an important entity especially in developing world. Measurement of serum [K+] and PChE may be helpful in predicting severe outcomes and prognosis in OP poisoning. Clinicians and medical toxicologists should consider hypokalemia associated with reduced PChE level as alarming signs of poor prognosis in OP poisoned patients.

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REFERENCES

1. Chitra GA, Muraleedharan VR, Swaminathan T, Veeraraghavan D. Use of pesticides and its impact on health of farmers in South India. Int J Occup Environ Health 2006;12:228-33.
2. Singh B, Gupta MK. Pattern of use of personal protective equipments and measures during application of pesticides by agricultural workers in a rural area of Ahmednagar district, India. Indian J Occup Environ Med 2009;13:127-30.
3. Pillay VV. Comprehensive Medical Toxicology. 1st ed. Hyderabad, Inida: Paras Publications; 2003.
4. Naik B, Hirshhorn S, Dharnidharka VR. Prolonged neuromuscular block due to cholinesterase depletion by plasmapheresis. J Clin Anesth 2002;14:381-4.

5. Prasad DRMM, Jirli PS, Mahesh M, Mamatha S. Relevance of Plasma Cholinesterase to Clinical Findings in Acute Organophosphorous Poisoning. Asia Pac J Med Toxicol 2013;2:23-7.
6. Worek F, Koller M, Thiermann H, Szinicz L. Diagnostic aspects of organophosphate poisoning. Toxicology 2005;214:182-9.
7. Kamanyire R, Karalliedde L. Organophosphate toxicity and occupational exposure. Occup Med (Lond) 2004;54:69-75.
8. Bhattacharyya K, Phaujdar S, Sarkar R, Mullick OS. Serum creatine phosphokinase: a probable marker of severity in organophosphorus poisoning. Toxicol Int 2011;18:117-23.
9. Proudfoot AT. Acute Poisoning: Diagnosis and Management. 2nd ed. Boca Raton, FL: CRC Press; 1993.
10. Vij K. Textbook of Forensic Medicine and Toxicology: Principles and Practice. New Delhi: Elsevier; 2008.
11. Mehta AB, Shah AC, Joshi LG, Kale AK, Vora DD. Clinical features and plasma acetylcholinesterase activity in poisoning with insecticidal organophosphorous compounds. J Assoc Physicians India 1971;19:181-4.
12. Balali-Mood M, Ayati MH, Ali-Akbarian H. Effect of high doses of sodium bicarbonate in acute organophosphorous pesticide poisoning. Clin Toxicol (Phila) 2005;43:571-4.
13. Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008.
14. Lin SH, Lin YF, Halperin ML. Hypokalaemia and paralysis. QJM 2001;94:133-9.
15. Stedwell RE, Allen KM, Binder LS. Hypokalemic paralyses: a review of the etiologies, pathophysiology, presentation, and therapy. Am J Emerg Med 1992;10:143-8.
16. Ober KP. Thyrotoxic periodic paralysis in the United States. Report of 7 cases and review of the literature. Medicine (Baltimore) 1992;71:109-20.
17. Lin SH, Lin YF. Propranolol rapidly reverses paralysis, hypokalemia, and hypophosphatemia in thyrotoxic periodic paralysis. Am J Kidney Dis 2001;37:620-3.
18. Cheng CJ, Kuo E, Huang CL. Extracellular potassium homeostasis: insights from hypokalemic periodic paralysis. Semin Nephrol 2013;33:237-47.