Short Communication

Hypokalaemia: Strong Predictor of Morbidity and Mortality in Acute Organophosphorus Compound Poisoning

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ABSTRACT

Mortality in organophosphorus compound (OPC) poisoning is mainly due to respiratory arrest as an end result of respiratory muscle paralysis. Associated hypokalaemia compounds the weakness. Potassium is firmly balanced in urinary excretion. Ratio between intracellular and extracellular potassium concentration plays a fundamental role in cell membrane resting membrane potential (RMP) maintenance. A relatively small change in extracellular potassium concentration can significantly alter RMP and functional activity.

This study is aimed at evaluating the significance of hypokalaemia in acute OPC poisoning and its implications as a predictor of morbidity and mortality. It is a 6-month, cross-sectional study, which included all cases admitted with a history of consumption of OPC, and confirmed at the Poison Detection Center, with exclusion of patients aged more than 60 years, presence of severe vomiting, and associated chronic illnesses, such as renal and cardiac failure. Serum potassium concentration was prospectively measured and tabulated along with associated clinical signs.

The study revealed that potassium homeostasis appears to be altered in acute OPC poisoning, which in turn alters neuromuscular junction activity. Gradual fall in potassium concentration produces serious clinical features, including muscle fasciculations, twitching, convulsions, respiratory distress and death. The severity of these was directly proportional to the reduction in the potassium level.

Key Words: OPC; organophosphorus compound; Rodenticide; Suicide; Zinc phosphide

INTRODUCTION

Morbidity and mortality due to poisoning is a worldwide problem. According to the World Health Organization, 3 million cases of pesticide poisoning occur every year, and an estimated 2 million people die; most of the deaths occur in Asia, and at least 50% are due to organophosphorous poisoning.[1] The total number of poisoning cases is constantly increasing in all developing and developed countries in all age groups, irrespective of sex due to various reasons. Accidental poisoning has become more common in children due to increased use of chemicals both in households and in agriculture.[2]

Pesticide poisoning in developing countries has high rate of morbidity and mortality as facilities are limited for early diagnosis and treatment. Most of the toxicity associated with exposure to organophosphorus compound (OPC) pesticides has been attributed to inhibition of the enzymes acetylcholinesterase and plasma cholinesterase in nerve, neuromuscular and glandular tissues, where these enzymes play a key role in cell to cell communication.[3]

Despite significant progress in understanding the potential mechanisms of toxicity far beyond the commonly accepted mechanism of cholinesterase inhibition in intentional exposure, the precise health effects following exposure are yet to be completely defined. The inhibition of cholinesterases by itself cannot account for the

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wide range of disorders that have been reported. It is becoming apparent that, although inhibition of cholinesterases plays a key role in the toxicology of organophosphates, individual susceptibility, the inhibition of other enzyme systems and the direct effects of organophosphates on tissues are also important.[4]

Electrolyte imbalance in many of these cases adds to the clinical burden, contributing to the morbidity and mortality. As a consequence of intracellular shift of potassium, due to re-entry, fatal cardiac arrhythmias in OPC poisoning may occur. This is the result of tissue hyperkalaemia and serum hypokalaemia. Distribution of potassium is affected by chronic illnesses, such as cardiac failure, renal failure and other factors (hormones, osmolality, disturbances in acid–base balance, etc). Factors like decreased intake, increased net loss by gastrointestinal tract or excessive sweating leading to integumentary loss and shift into intracellular compartment can also result in hypokalaemia.[5] As potassium is the major intracellular cation, the ratio between intracellular and extracellular potassium concentrations (38:1), plays a crucial role in cell membrane resting potential (RMP) maintenance.[5] Thus, RMP and cellular excitability will be significantly altered even with relatively small change in the extracellular potassium concentration. The normal neuromuscular function entirely depends on the extracellular potassium concentration.

Literature surveys reveal little about hypokalaemia in acute OPC poisoning. Thus, we aimed to study the significance of hypokalaemia in relation to clinical manifestations in cases of acute OPC poisoning.

MATERIALS AND METHODS

After obtaining the approval of the institutional Ethical Committee on Human Studies and informed consent of the patients, this double-blind, clinical, cross-sectional study was conducted at KLE's Dr Prabhakar Kore Medical and Research Center, Jawaharlal Nehru Medical College, Belgaum, Karnataka from November 2009 to April 2010. The gastric aspirate samples of patients with history of consumption of OPC pesticides was tested in the Poison Detection Center, Dept of Forensic Medicine & Toxicology, by thin layer chromatography and UV-Vis spectrophotometry, and following confirmation were included in the study. Cases with severe vomiting and those associated with chronic illnesses, such as renal and cardiac failure were excluded from the study as these conditions are often associated with altered potassium levels.

Pre-interventional routine investigations and serum electrolyte assay were done using venous blood in 50 consecutive patients. The potassium level was estimated using C311 fully automated biochemistry analyser, wherein 3–5 mL of blood was subjected to centrifugation and the plasma was separated. 25 µL of plasma was added to 25 µL of reagent and subjected to potassium estimation. Thus, the values at the time of admission of all the patients included in the study were assessed. Potassium level of less than 3.5 mmol/L was considered as hypokalaemia.[6] Serious clinical features, such as fasciculations, muscle weakness, respiratory distress and convulsions were noted. Ventilators were used in cases where there was respiratory failure. The criteria for the diagnosis of respiratory failure and ventilator support were based on the following:[7]

- Apnoea
- Ovious hypoventilation
- Persistent cyanosis dispite oxygen supplementation
- Persistent tachypnoea - respiratory rate >24/min
- Persistent oxygen saturation level <90% with oxygen supplementation by non-invasive means
- Active involvement of accessory muscles of respiration.

The clinical status of the patients was assessed and tabulated.

RESULTS

There were 50 cases of OPC poisoning in the median age group of 27.14 years. Out of these, 1 case was occupational, 7 cases were accidental, and 42 were suicidal in nature. A total of 13 cases presented with hypokalaemia (average potassium level of 3.11) along with one or more significant clinical features (**Table 1**). However, there were some cases, which showed serious clinical features without absolute hypokalaemia (< 3.5 mmol/L). Monocrotophos was the most common type of OPC detected.

DISCUSSION

OPCs are used around the world as pesticides because of affordability and effectivity. However, suicidal and accidental ingestion of OPC pesticides has become rampant, especially in developing countries such as India. They are readily absorbed following ingestion, and via the skin, following prolonged dermal contact. Toxicity is expressed when the OPC binds to acetylcholinesterase, preventing hydrolysis and resulting in an accumulation of acetylcholine in the synaptic cleft.

Mahdi Balali-Mood et al suggested that hypokalaemia is the main cause for the muscular weakness seen in such cases of OPC poisoning.[8] In our study, 17/50 patients revealed muscle weakness and fasciculations with an average serum potassium level of 3.32 +/- 0.11. When the potassium level decreased below 3.5 mmol/L, serious clinical features developed. At the mean level of +/- SEM [K^+] 3.32 +/- 0.11 mmol/L, the patients developed fasciculations and muscle twitching in association with steady decrease in oxygen saturation level, and gradually progressed to respiratory distress to such a level that there was requirement of ventilatory support (mean level of +/- SEM [K^+] 3.28 +/- 0.10 mmol/L). When the mean concentration reduced drastically to 2.90 +/- 0.06 mmol/L, the patients died. In all these cases, the *p value* was less than 0.0001.

Some patients presented with convulsions with a mean level of +/- SEM [K^+] 3.83 +/- 0.12 m mol/L. However, the *p value* in these cases was insignificant (**Table 2**). Potassium homeostasis is known to be altered in acute OPC poisoning. Alteration in potassium concentration may alter neuromuscular junction activity and contributes to overall morbidity and mortality. The patients in the present study developed serious clinical signs and symptoms sequentially as the serum potassium concentration reduced. With progressive fall of potassium concentration, the following features occurred: muscle weakness, fasciculations, twitching, convulsions, respiratory distress and death. The decrease in serum potassium concentration was thus directly proportional to the onset of significant signs and symptoms.

Table 1 Patients with Potassium Concentrations and Associated Clinical Features

Patient's serial no.	[K^+] in mmol/L	Muscle fasciculations and muscle weakness	Respiratory distress	Convulsions	Mortality
08	2.8	+	+		+
10	4.0			+	
13	3.4	+	+		
16	3.1	+	+		
18	3.0	+	+		+
19	3.8	+	+		
20	2.8	+	+		
21	3.5	+			
22	2.8	+	+		+
24	3.9	+	+		
25	3.3	+	+		
27	4.6	+			
35	3.6	+	+	+	
37	3.8		+		
39	3.0	+			+
40	3.3	+	+		
41	3.0	+	+		
46	3.9			+	
47	3.3	+	+		
50	3.2	+			
		17	**14**	**3**	**4**

Potassium ion is tightly balanced, in that urinary excretion (1–1.5 mmol/kg/day) is directly proportional to the total body potassium, and is a good marker of total body potassium.[6] The resting membrane potential and functional activity of electrically excitable cells undergo significant alteration even due to minute changes in the extracellular potassium concentration. In acute cases of OPC poisoning, due to strong nicotinic actions, respiratory distress, muscle weakness and paralysis set in. In such stressful conditions, hypokalaemia gets established, which adds to the clinical burden, and/or these signs and symptoms get aggravated in the presence of associated hypokalaemia. Hypokalaemia presents with lassitude, muscular weakness, loss of deep tendon reflexes, paralysis and death will be sudden, which is usually due to respiratory distress, a complication of respiratory muscle weakness and paralysis. Cause of death in both acute OPC poisoning and hypokalaemia is due to muscular weakness and respiratory distress. It is not uncommon for patients to present to the emergency room with severe weakness and a markedly low plasma potassium concentration.[9]

Hypokalaemia and paralysis are potentially reversible medical emergencies.[10] Morbidity and mortality are related to complications secondary to hypokalaemia, such as cardiac arrhythmias or respiratory failure.[11] Although there are many potential causes of hypokalaemia, there are far fewer entities in the differential diagnosis of hypokalaemia and paralysis.[10] Hypokalaemia and paralysis can be divided into 2 types: hypokalaemic periodic paralysis due to a short-term shift of potassium into cells,[12–14] and non-hypokalaemic periodic paralysis resulting from a large deficit of potassium.[15,16] The differential diagnosis in a patient with hypokalaemia and paralysis can be challenging, but it is important to make the diagnosis promptly because different therapies are required for each type.

Organophosphates induce cardiac toxicity in a significant way by elongation of the repolarization period in the ventricles. This is clinically marked and measured in electrocardiogram as long QT syndrome. The primary membrane currents responsible for this condition are two in number. Potassium modulation of the sodium current and reduction of the potassium currents mimic the experimentally observed change in slope of the depolarization in the presence of organophosphates as well as the prolongation and shape of repolarization. This is a precursor to the onset of torsades de pointes and ventricular fibrillation, the fatal complications due to alteration in potassium concentration. Animal experimental data show that OPC intoxication results in lesions of the cardiac tissue, acidosis and anoxia. These effects in terms of the membrane currents can be expressed and simulated by ion channel conductivity changes. Potassium conductivity changes, which can be caused by ligand blocking the channel, are a major contributor to increased cycle length and consequently long QT syndrome.[11]

The hypokalaemia in acute OPC poisoning and the associated serious features is an alarming and strong predictor of morbidity and mortality. During the whole course of treatment, the treating physician should watch the serum potassium concentration, and maintain it at normal levels to prevent unexpected mortality.

CONCLUSION

Hypokalaemia is a relatively common and alarming sign in acute OPC poisoning, and carries with it a high risk of

Table 2 Mean Potassium Concentration in Relation to Clinical Picture

Sl. no	Clinical features	Observation	Mean +/-SEM [K^+] in mmol/L	p-value
1.	Fasciculations & muscle twitching	Present	3.32 +/- 0.11	< 0.001
		Absent	4.02 +/- 0.08	
2.	Respiratory distress	Present	3.28 +/- 0.10	< 0.001
		Absent	3.97 +/- 0.085	
3.	Convulsion	Present	3.83 +/- 0.12	< 0.82
		Absent	3.77 +/- 0.06	
4.	Mortality	Present	2.90 +/- 0.06	< 0.001
		Absent	3.85 +/- 0.08	

mortality. It is simple and economical to investigate potassium levels, and can serve as a powerful marker of morbidity and mortality in acute OPC poisoning.

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