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Association between ECG Alterations and Outcomes of Patients with Acute Organophosphate Poisoning

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Running title: ECG Alterations and Outcomes of Acute Organophosphate Poisoning

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Abstract

Background: Organophosphate (OP) poisoning leads to atrioventricular node blockade, alterations in ST segment, prolongation of QT interval, alterations in P wave, lethal arrhythmias, and cardiac arrest through the inhibition of acetylcholinesterase and consequent accumulation of free synaptic acetylcholine level. So the present study was aimed to investigate the role of ECG monitoring combined with the introduction of anti-arrhythmic interventions on OPs poisoning outcomes.

Methods: 41 patients with OPs poisoning were included. Patients with history of heart or liver diseases, cholinesterase deficiency, anemia, and poisoning with other toxins were excluded. Demographic characteristics, the time elapsed between OP ingestion and hospital admission, need for mechanical ventilation, and serum cholinesterase level were recorded. ECG of patients was analyzed for rate, rhythm, ST-T abnormalities, conduction defects, and measurement of PR and QT intervals. Study outcomes were measures of morbidity and mortality.

Results: Of 41 patients, with mean age of 34.76±13 years, 19 were male. For 68.3% of the patients, the time elapsed between ingestion and hospital admission was 3-6 hours. 8 patients were treated with mechanical ventilation. There was a significant correlation between ST segment alterations and poisoning outcomes including uncomplicated discharge, complicated discharge, and death (P=0.02). 31 patients were discharged without any complication, 8 with morbidity and 2 expired. ST segment changes were seen in 4 patients. 2% had PR interval greater than 0.21s and 3% had QT interval longer than 0.45s. The mean serum cholinesterase concentration was 3011.56 U/L.

Conclusion: Due to lethal cardiac arrhythmia caused by OP poisoning, continuous monitoring, managing, and preventing irreparable effects of OP poisoning is highly emphasized.

Keywords: Acetylcholinesterase; Arrhythmia; Morbidity; Mortality; Organophosphate

Introduction

Organophosphate (OP) pesticides are the most extensively used insecticides, particularly in rural or undeveloped parts of developing countries.[1] Approximately two hundred thousand persons die from OP pesticide poisoning annually, and the rate of mortality is generally greater than 15%.[2] These pesticides are progressively used as suicide substance with an increasing rate of mortality during the recent years.[3] OP pesticides are phosphoric or phosphonic acid derivatives that irreversibly inhibit acetylcholinesterase by binding to its zymolysis site and form phosphorylated

acetylcholinesterase, leading to the accumulation of acetylcholine. Therefore, the cholinergic nerve is stimulated, and a varieties of symptoms appear.[4,5] The main SLUDGE signs of OPs poisoning are salivation, lacrimation, urination, defecation, gastrointestinal upset, and emesis.[6] The cardiac manifestations of OPs poisoning occur in a majority of affected patients and may range from harmless electrocardiographic (ECG) changes such as sinus tachycardia, to life-threatening complications such as cardiogenic pulmonary edema. Additionally, OPs poisoning leads to atrioventricular (AV) node blockade, alterations in ST segment, prolongation of QT interval, alterations in P wave, lethal arrhythmias, and cardiac arrest through the inhibition of acetylcholinesterase and consequently increased synaptic accumulation of free acetylcholine level. The most fatality of OP poisoning results from respiratory failure.[7]

The clinical manifestations of damage caused by OPs pesticides to the myocardium vary among patients, which include heart failure, cardiogenic shock, arrhythmia, and sudden death. The association between arrhythmias and the level of serum cholinesterase concentration has been investigated extensively,[8] and alterations in heart tissue have been found in post-mortem samples of OPs poisoning patients.[3] On the other hand, treatment of OPs poisoning with atropine can potentially induce lethal arrhythmias.[4,5]. It seems that careful ECG monitoring for detection of abnormal heart rhythms and subsequent implementation of an appropriate treatment modality to prevent from life-threatening arrhythmias can play a pivotal role in assessment and saving the lives of OPs poisoning patients.[9-11] Therefore, the present study was aimed to investigate the role of ECG monitoring combined with the introduction of anti-arrhythmic interventions on OPs poisoning outcomes including morbidity and mortality.

Materials and Method

This study was conducted as a cross-sectional research since 1 January 2016 to 15 December 2016. 41 patients with OPs poisoning who were referred to Sina Hospital, a referral poisoning hospital affiliated with Tabriz University of Medical Sciences, were included. Age, sex, marital and educational status, type of OP compound used, psychosocial history, the time elapsed between ingestion and hospital admission, level of consciousness at the time of admission, need for mechanical ventilation, and serum cholinesterase level were recorded from the medical files. For all patients, ECG was recorded daily in the poisoning ward and analyzed for rate, rhythm, ST-T abnormalities, conduction defects, and measurement of PR and QT intervals. Study outcomes were measures of morbidity and mortality. Patients' morbidity was defined as uncomplicated discharge

and complicated discharge. Patients were excluded if they had history of heart or liver diseases, cholinesterase deficiency, anemia, and poisoning with other toxins in addition to OPs pesticides. A minimum required number of patients to draw strong conclusion with a 95% level of certainty and statistical power level of 80% was estimated to be 41 patients.

Data were expressed as frequency (%) or mean ± SD and analyzed descriptively by SPSS statistical software, version 20 (SPSS Inc., Chicago). The chi-square or Fisher's exact test was used to find any correlation between two qualitative variables including ST segment alterations and poisoning outcomes. P value of less than 0.05 was considered statistically significant. The purposes of the research were explained and clarified for all patients and a written informed consent form was signed by all patients before entering the study. Moreover, identity and clinical data of patients remained anonymous along the study.

Results

From 73 patients who were referred to our center, 32 patients were excluded from the study due to their comorbid heart (10) and liver diseases (8), anemia (3), and poisoning with other toxins in addition to OPs pesticides (11). Of 41 patients, with mean age of 34.76±13 years (14-68 years), 19 were male and 22 were female. There was a statistically significant proportion of married individuals in female than male patients (P=0.03). Moreover, distribution of educational status was significantly different among poisoned patients (P=0.02) (Table 1).

Table 1. Demographic characteristics of organophosphate poisoned patients

Variable			**Frequency**	**P-value**
Sex, n(%)	Female		22 (53.7)	P=0.6
	Male		19 (46.3)	
Marital Status, n(%)	Single	Female	6 (14.63)	P=0.03
		Male	9 (21.95)	
	Married	Female	16 (39.02)	
		Male	10 (24.39)	
Educational Status, n(%)	Illiterate		4 (9.8)	P=0.02
	Elementary		11 (26.8)	
	Associate degree		20 (48.8)	
	Bachelor degree		6 (14.6)	

For 68.3% of the patients, the time elapsed between ingestion and hospital admission was 3-6 hours. Among OPs compounds, malathion was the most common cause of poisoning (31.7%). On the other hand, there was no equal distribution among various types of OPs (Table 2).

Table 2. Types of OP compound ingested

Compound Type	Number	Frequency (%)	P-value
Malathion	13	31.7	P=0.001
Metathione	6	14.6	
Parathion	6	14.6	
Phosphamidon	3	7.3	
Dimethod	1	2.4	
Fenitrothion	1	2.4	
Other	11	26.8	

73.2% of patients had an ED Glasgow Coma Scale (GCS) score of ≥ 13 at the time of admission (Table 3). 8 patients were intubated and treated with mechanical ventilation. Based on medical interview, patients' history was remarkable for psychological disorder (48.8%), substance abuse (34.1%), and suicidal attempt (26.8%). 75.6% of patients (31 subjects) were discharged without any complication, 8 with morbidity and 2 patients expired.

Table 3. Level of consciousness in OPs poisoned patients

Level of consciousness	Number	Frequency (%)
Conscious	30	73.2
Lethargy	6	14.6
Obtundation	3	7.3
Coma	2	4.9
Total	41	100

There was a significant correlation between ST segment alterations and poisoning outcomes including morbidity and death (P=0.02). ST segment changes were seen in 4 patients. Among patients, 2% had PR interval greater than 0.21s (0.08-0.24s) and 3% had QT interval longer than 0.45s (0.2-0.48s) (Table 4). The mean serum cholinesterase concentration was 3011.56 U/L with a minimum level of 132 U/L and maximum level of 8756 U/L.

Table 4. Values of ECG changes in patients with acute OPs poisoning

Variable	Values	n (%)
PR (s)	≤0.12	16 (39.9
	0.13-0.2	23 (56.1)
	≥0.21	2 (4.9)
QT (s)	≤0.36	28 (68.3)
	37-44	10 (24.4)
	≥0.45	3 (7.3)

Discussion

Findings of the present study showed that there is significant relationship between ECG changes and the OPs poisoning outcomes. This finding is consistent with the reports of Atli's study.[12] However, in a retrospective study by Chen et al, exploring the risk factors for acute myocardial injury following acute OP pesticide poisoning, frequent ectopic beats, rapid atrial arrhythmia, rapid ventricular arrhythmia, and ST-T changes were the most common features of ECG changes among OP poisoned patients with a significantly higher incidence in the patients with acute myocardial injuries. In addition, the serum acetylcholinesterase level was markedly lower in the patients with acute myocardial injuries compared to the control group.[13] Balouch reported that ECG alterations are associated with cardiac complications in almost 78% of OPs poisoned patients.[10] Rahbar-Taromsari et al performed a retrospective descriptive study on 100 OP poisoned patients to investigate ECG manifestations of poisoning. About 63% of study patients showed ECG alterations, as sinus tachycardia (31%), nonspecific ST-T change (24%), prolonged QTc interval (3%), and conduction disturbances (13%).[14] Prolonged QT segment was witnessed in merely 3% of subjects involved in our study. Other studies have also shown QT interval prolongation approximately in 55.5% of OPs poisoned patients.[9,15] Other ECG changes including elevation of ST segment, inversion of T wave and prolongation of PR interval have been reported as ECG characteristics of first-degree atrioventricular block in patients with OPs poisoning.[16] Although cardiotoxicity mechanisms by OPs are still uncertain,[15,17] it may occur in 3 phases. First, a brief phase of sympathetic overactivity causes tachycardia and hypertension. Second, an extended period of cholinergic crisis develops during which hypotension and bradycardia together with ST-T changes and dangerous arrhythmia can occur. Third phase is longer and usually characterized

by QT interval prolongation and polymorphic ventricular tachycardia which can lead to sudden death.[18] Prolongation of PR interval and changes in ST-Segment-T-wave occurred in 2 and 4 respectively in our study patients. Makwana et al conducted a prospective descriptive study on 50 OP poisoned patients to determine various ECG changes and their importance in acute OP poisoning. 70% of their study patients developed ECG alterations including sinus tachycardia (24%), sinus bradycardia (8%), QT prolongation (12%), PR prolongation (2%), ST elevation (8%), T inversion (8%), atrial fibrillation (2%), ventricular tachycardia (2%), and extrasystole (4%).[19] This finding was consistent with our study results, but with different proportions of arrhythmias. Additionally, Vijayakumar et al reported 20 suicidal cases with large dose acute OPs poisoning who had ECG abnormalities as follows: Prolonged QTc (60%), elevated ST segment (40%), T wave inversion (40%), sinus tachycardia (60%), and sinus bradycardia (10%). Thus, OP compound ingestion can cause marked ECG changes such as non-specific ST-T changes and QTc prolongation. As prolonged QTc can lead to lethal arrhythmias, careful monitoring of the ECG of the patients with OPs poisoning is necessary.[20] On the other hand, since there is a marked relation between low levels of cholinesterase and patient mortality in severe OPs poisoning,[12] serial measurement of cholinesterase level is of prognostic value in patients with OPs poisoning.[21] Our study had some limitations which included small size of studied sample, single center involvement, inadequate number of measurements of serum cholinesterase concentration during the patients' hospitalization and thus inability to assess any association between serum cholinesterase concentration and ECG changes, inability to longer follow up patients who discharged with morbidity.

Conclusion

Our study showed marked relationship between ECG changes and OPs poisoning outcomes. Due to drastic morbidity and mortality caused by cardiac arrhythmias resulting from Ops poisoning, continuous monitoring and controlling as well as preventing and managing life-threatening arrhythmias can be life-saving for OPs poisoned patients.

Conflict of interests

The authors claim that there is no conflict of interest.

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