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Emergency Laboratory Abnormalities in Suicidal Patients with Acute Organophosphate Poisoning

[İntihara Teşebbüs Eden Akut Organofosfat Zehirlenmeli Hastalarda Acil Laboratuvar Anormallikleri]

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ABSTRACT

Purpose: Organophosphate poisoning may cause the life-threatening events resulted in different organ failure. The aim of this study was to evaluate the relationship between laboratory parameters and the degree of intoxication in patients attempted to suicide using organophosphate admitted to the emergency department.

Material and methods: Ninety-one patients who attempted to suicide with acute organophosphate poisoning admitted to the emergency service were included in this retrospective study. The initial laboratory findings and clinical status of patients were evaluated. Clinical severity of patients was also graded according to the Bardin classification on admission.

Results: Oral ingestion was found to be the most common route of poisoning for suicidal purpose. Serum cholinesterase activity was measured significantly depressed in the grade 1, 2 and 3. Leukocyte counts, glucose and amylase levels were significantly higher in the grade 1 and 2, but they were considerably elevated in the grade 3 compared to normal reference. Acute renal failure and pancreatitis were observed on following admission in some patients of grade 2 and 3. Six patients were died in these grades.

Conclusions: The marked decrease of serum cholinesterase activity appears to be associated with clinical severity in patients with acute organophosphate intoxication. However, it must be interpreted carefully due to intake of different organophosphate and the amount of exposure. Hyperglycemia, hyperamylasemia and leukocytosis can arise frequently in patients of grade 2 and 3.

Key Words: organophosphates, poisoning, suicide, cholinesterase

ÖZET

Amaç: Organofosfat zehirlenmesi yaşamı tehdit eden olaylara neden olabilir. Çalışmanın amacı; acil servise kabul edilen organofosfat kullanarak intihara teşebbüs eden hastalarda intoksikasyon derecesi ve laboratuar parametreleri arasındaki ilişkiyi değerlendirmekti.

Materyal ve Metod: Bu retrospektif çalışmaya 91 hasta dahil edildi. İlk laboratuvar bulguları (serum kolinesteraz, aspartat transaminaz, alanin transaminaz, total ve indirekt bilirubin, amilaz, glukoz, kreatinin ve lökosit sayımı) ve hastaların klinik durumu değerlendirildi. Ayrıca hastaların klinik şiddeti kabul esnasında Bardin sınıflandırmasına göre derecelendirildi.

Bulgular: İntihar amacı ile zehirlenmenin en yaygın yolu oral alınım olarak bulundu. Serum kolinestraz aktivitesi safha 1,2 ve 3'de istatistiksel olarak baskılanmış ölçüldü. Lökosit sayımı, glukoz ve amilaz düzeyleri safha 1 ve 2'de anlamlı olarak yüksekti. Bunların düzeyleri safha 3'de normale göre oldukça yüksekti. Safha 2 ve 3'ün bazı hastalarında yatışı mütakip akut böbrek yetmezliği ve pankreatitis gelişti. Safha 2 ve 3'de 6 hasta gözlem süresince tüm çabalara rağmen öldü.

Sonuçlar: Serum kolinesteraz aktivitesinde azalma, akut organofosfat intoksikasyonlu hastalarda intoksikasyonun klinik şiddeti ile ilişkili gözükmektedir. Bununla birlikte serum kolinesteraz aktivitesi, farklı organofosfat alımı ve miktarına bağlı olarak dikkatli ilişkilendirilmelidir. Hiperglisemi, hiperamilazemi ve lökositozis safha 2 ve 3 hastalarda sıklıkla ortaya cıkabilir.

Anahtar Kelimeler: organofosfatlar, zehirlenme, intihar, kolinesteraz

Introduction

Organophosphates (OPs) are toxic substances which frequently cause intoxication in human [1]. The toxic effects of these compounds are the consequence of the inhibition of acetylcholinesterase in the nervous system, leading to an accumulation of the neurotransmitter acetylcholine at synapses and myoneural junctions and then the continued over stimulation of acetylcholine receptors. Thus, the clinical symptoms begin in patients after intake of the toxic agent. Intoxication with insecticides or pesticides containing OPs occurs either as a result of accidental or suicidal use of the agents. Organophosphate poisoning (OPP) cases constitute a great percentage of suicide patients in Turkey as well as in many developing countries [2]. Intoxication with OPs is generally a serious condition for patients in the emergency medicine or intensive care. It is known that physicians should be on alert for diagnosis and treatment of OPP.

Poisoning with OPs shows extremely heterogeneous pictures of cholinergic crisis frequently associated with clinical complications [3]. In acute poisoning, the severity of symptoms parallels the degree of acetylcholinesterase (AChE) activity [4]. In literature, there are prognostic scoring systems such as the APACHE (Acute Physiology and Chronic Health Evaluation) and SAPS (Simplified Acute Physiology Score) [5], the grading of organophosphate intoxication done by Namba et al [6], and Bardin et al [7] for the evaluation of intoxication. The clinical classification of the patients on admission to the Emergency Department (ED) may be helpful in assignment of treatment strategies and estimation of the prognosis. For this purpose, Bardin classification for OPP (Table 1) seems convenient to be used in the ED. Although usefulness of this classification in the early assessment of patients with OPP has less reported, the Bardin grading may facilitate the recognition of seriously poisoned subjects to permit their early admission to an intensive care unit or ED for emergency treatment [7,8].

It is frequently known that human attempted to suicide can ingest an excessive suicidal agent and/or be injected it into own body. OPP may cause an acute organ failure due to toxicity, in particularly suicidal cases. Also, the toxicity of OPs causes adverse effects on tissues and organ function [9-12]. Both clinical features and laboratory parameters are very important for accurate diagnosis in poisonings. Moreover, laboratory confirmation of the diagnosis may be necessary in order to provide optimal patient care. Emergency laboratory tests may give information about first acute organ damage and the degree of poisoning in patients with acute OPP. The purpose of this study was to investigate the relationships between the initial emergency laboratory parameters and degree of organophosphate intoxication in patients attempted to suicide in the ED on admission.

Table 1. The degree of organophosphate intoxication [7,8]

Grade 0: No clinical manifestations
Grade 1: Hypersecretion, fasciculations, consciousness
Grade 2: Grade 1 + hypotension, unconsciousness
Grade 3: Grade 2 + stupor, abnormal chest x-ray, $pO_2 < 10$ mmHg

Materials and Methods

Patients

Local ethical committee approved procedures used in this study. This study was completed retrospectively. Patients with OPP who attempted to suicide were admitted to the ED of Ondokuz Mayıs University in Samsun, Turkey between April 2006 and March 2009. In addition, patients' clinical and laboratory findings were obtained from the patient file on admission. Patients were evaluated at the time of admission in the ED. A detailed history had been taken from the patient, accompanier person or patient's family. During the study period, we selected to evaluate merely the patients who intended to commit suicide with organophosphate agents and graded these patients regarding clinic findings in relation to Bardin classification [7]. As indicated in Table 1, patients were graded (grade 0, 1, 2, 3) according to clinical findings on admission in acute organophosphate intoxication. Ninety-three patients were included in this study. The patient who had any disease or other pathologic states such as infection, use of drugs, hematological and organ disorders prior to poisoning and the patients with accidental poisoning were excluded from the study. Two patients were diagnosed with diabetes mellitus prior to poisoning, and thus their laboratory findings were out of the statistical analysis in our study as well. Some information about patients was shown in Table 2 and 3.

The diagnosis of acute OPP in patients was based on the following criteria: (A) ingestion of insecticides/pesticides or intra-venous/muscular injection of OPs, (B) characteristic clinical signs and symptoms of OPP, (C) decreased serum cholinesterase activity. After the diagnosis, in addition to general supportive measures (i.e. washing of the whole skin surface, gastric lavage, administration of cathartics and activated charcoal), a standard therapy method with atropine and pralidoxime was given to the patients. Either continuous infusion or an intermittent dose of atropine was administered until bronchial secretions were controlled. Pralidoxime was administered as from 2 g daily (divided into four doses) up to 200–500 mg/hr (continuous infusion) according to the clinical severity of the condition. All of the patients were observed in emergency intensive care unit and clinical outcome was also noted.

Laboratory Parameters

The initial emergency laboratory parameters: Serum cholinesterase (SChE, Method with S-butyrylthiocholine iodide. Cholinesterase catalyzes the hydrolysis of S-butyrylthiocholine iodide to thiocholine iodide and

Table 2. Initial symptoms/signs in individual patients

Initial symptom/sign	**Percentage of cases** (n = 93)
Vomiting and Nausea (%)	50 (53.7)
Altered consciousness (%)	26 (27.9)
Dyspnea (%)	10 (10.7)
Weakness (%)	4 (4.3)
Fogging (%)	3 (3.2)

Table 3. Some characteristics of patients with acute OP according to grades

	Grade 1	**Grade 2**	**Grade 3**	**Total**
Sex Women	34	10	4	48
Men	24	14	5	43
Total Count	58	24	9	91
Age Mean ± SD	34.43 ± 16.92	39.75 ± 18.33	51 ± 17.48	
Median (Min; Max)	34 (18;76)	34.5 (18;80)	49 (30;88)	
Mode of poisoning	Suicidal attempt	Suicidal attempt	Suicidal attempt	
Means of exposure	Intra-muscular injection(one patient), Oral intake	Intra-muscular injection(one patient), Oral intake	Oral intake	

butyrate. Thiocholine iodide reacts with 5,5'-dithiobis-2-nitrobenzoate and forms the yellow colored product 5-mercapto-2-nitrobenzoate. The rate of formation of this product is directly proportional to the catalytic cholinesterase activity. It is determined by measuring the increase in absorbance at 480 nm. Abs. calculation mode: kinetic. Precision: reproducibility was determined using human samples and controls in an internal protocol. Mean values: level 1; 1728 U/L, level 2; 9545 U/L. CV within run: 1.0 % (level 1), 0.99 % (level 2). CV between run: 2.2 % (level 1), 1.8 % (level 2). Analytical sensitivity: 4.5 U/L, creatinine, glucose, amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and indirect bilirubin levels were determined by Cobas Integra 800 and Roche Diagnostics reagents, and complete blood count (WBCs) was measured by Beckman Coulter GENS in the emergency laboratory. Also, the other emergency tests were determined in patients such as chest x-ray, blood gases after clinical assessment.

Statistical Analysis

Data have been analyzed by Kolmogorov-Smirnov test for the normality assumption of all measurements. They were not meeting the assumption, so non-parametric statistical methods were used to evaluate data. The groups were compared by using Kruskal-Wallis analysis of variances; pairwise comparisons were done by Mann-

Whitney-U test with Bonferroni correction. The mean ± Standard Deviation (SD) and median (min, max) values were given as descriptive statistics in Table 4. A P-value of <0.05 was regarded as statistically significant.

Results

The most common OPs exposed as a suicidal agent were methamidophos, parathione-methyl, folidol, 2,2-dichlorovinyl dimethyl phosphate, and fenthion. Mean arrival time of the patients to the ED from urban and rural areas after poisoning was 3.8 ± 3.2 hours (range, 2-14). The results of emergency laboratory on admission are shown in Table 4. SChE levels in patients of grade 3 was found to be significantly lower than in the grade 2 and 1 (P=0.044, P<0.001), similarly its value in the grade 2 was lower than in the grade 1 (P=0.008). SChE activity accepted as normal is between 5.400 and 13.200 U/L in the emergency laboratory. Statistically significant difference was obtained for AST and ALT determined between the grades, however reference of these parameters is 8–46 U/L and 7–46 U/L. No statistically significant difference was obtained for total and direct bilirubin. Amylase levels were higher in the patients of grade 2 and 3 than in the patients of grade 1 (P<0.001, P<0.004). Glucose concentration was found to be the highest in the grade 3 and higher in the grade 2 compared to grade 1 (P<0.001). A significant difference was obtained for creatinine values between the grades, but its reference range is 0.4–1.4 mg/dl. WBCs in the patients of grade 1, 2 and 3 were measured over reference count (P<0.001).

It is note that serum creatinine level was increased (>1.4 mg/dl) in two patients in the grade 2 and four patients in the grade 3. As a result of elevation of creatinine which is a test for the kidney function, acute renal failure was arisen on following days in these patients of grade 2 and 3. Serum amylase level was elevated (>100 U/L) in sixteen patients of grade 1 at first day admission, however it was found pretty high in twenty-five patients of grade 2 in particularly ten patients of grade 3 according to the reference value. So, acute pancreatitis was occurred on following days in three patients of grade 2 and 3. AST level was high in four patients of grade 1, five patients of grade 2 and three patients of grade 3 regarding the reference. ALT level was high in one patient of grade 1, two patients of grade 2 and 3 regarding the reference.

Patients with OPP who received the standard therapy options promptly, mostly recovered from acute intentional poisoning in emergency intensive care unit. Nevertheless, two patients in the grade 2, four patients in the grade 3 died due to sudden respiratory and cardiac arrest, respiratory failure, CNS depression and the other causes.

Discussion

Ingestion of OPs for suicidal purposes is a major problem, especially in developing countries. OPP is associated with a high morbidity and mortality among patients admitted to emergency departments [2,11,24]. Symptoms of acute OPP develop during or after exposure. OPs not only affect AChE but also may alter the liver, kidney, pancreas and the other organ functions. The systems that might be affected by an organophosphate toxic agent are the urinary system, immune system, pancreas, liver, lungs, and the others, owing to hematological and biochemical changes as well [1,4,7-13]. At the same time, OPs inhibit AChE and SChE enzymes. The latter enzyme inhibition appears not to result in clinical manifestations [18].

Table 4. Emergency laboratory values on first day admission in organophosphate poisoning

	Grade 1 (n:58)	**Grade 2** (n:24)	**Grade 3** (n:9)	
Parameters	Mean ± SD Median (Min; Max)	Mean ± SD Median (Min; Max)	Mean ± SD Median (Min; Max)	P*
Serum Cholinesterase (U/L)	[a]2892.4 ± 2458.8 2208.5 (152; 9126)	[b]1329.0 ± 1250.2 919.0 (87;5079)	[c]593.4 ± 422.5 450.0 (150; 1603)	<0.05
Aspartate aminotransferase (U/L)	[a]24.68 ± 12.51 20.95 (12.00;70.00)	[b]34.46 ± 21.37 25.50 (3.0; 88.00)	[b]46.00 ± 34.70 32.00 (16.00; 124.00)	<0.05
Alanine aminotransferase (U/L)	[a]18.34 ± 12.27 15.00 (4.10; 79.80)	[b]22.11 ± 1036 18.50 (4.50; 47.00)	[b]27.77 ± 19.33 22.00 (8.00; 62.00)	<0.05
Total Bilirubin (mg/dl)	0.4805 ± 0.2378 0.4000 (0.19; 1.30)	0.6454 ± 0.4036 0.5700 (0.20; 2.19)	0.4667 ± 0.0866 0.5000 (0.30; 0.60)	>0,05
Direct Bilirubin (mg/dl)	0.0667 ± 0.0551 0.060 (0.01; 0.32)	0.1254 ± 0.1983 0.060 (0.01; 0.96)	0.0811 ± 0.0333 0.080 (0.04; 0.15)	>0,05
Amylase (U/L)	[a]94.82 ± 114.60 59.5 (23.0; 800.0)	[b]277.33 ± 272.21 195.0 (38.0; 1069.0)	[c]552.22 ± 351.07 420.0 (162.0; 1275.0)	<0.05
Glucose (mg/dl)	[a]124.5 ± 56.2 100.5 (58.0; 353.0)	[b]184.6 ± 90.1 160.5 (105; 536)	[b]224.1 ± 123.7 148.0 (126.0; 501.0)	<0.05
Creatinine (mg/dl)	[a]0.70 ± 0.17 0.69 (0.40; 1.07)	[b]0.94 ± 0.42 0.85 (0.50; 2.50)	[b]1.04 ± 0.38 0.90 (0.60; 1.60)	<0.05
WBCs ($10^3/\mu L$)	[a]11571.9 ± 3484.1 11350 (4570; 21600)	[b]18041.6 ± 6082.1 17100 (5700; 30900)	[b]21497.7 ± 4137.8 19800 (16500; 30000)	<0.05

*The different letters indicate statistically significant groups (p<0.05).

The classical laboratory tests for organophosphate toxicants are inhibition of serum/plasma cholinesterase and/or red blood cell AChE enzyme activities in blood. The enzyme depression is generally apparent within a few minutes or hours of significant absorption of organophosphate [4]. Also, decreased cholinesterase activity correlated with a higher APACHE score [14]. In literature, there is still a matter of debate whether the value of depression of SChE activity is a prognostic indicator or not in patients in the acute phase of OPP owing to evaluate the severity of intoxication [14-17]. In our study, SChE levels in blood were statistically suppressed by 54 % in the grade 2 and 79.5 % in the grade 3 with respect to the grade 1. Its value decreases gradually in patients from the grade 1 to the grade 3. These results may indicate the severity of poisoning on admission in patients of grade 1, 2, and particularly in grade 3 who measured much more depressed SChE activity when compared to normal as shown in Table 4 and Figure 1. As a result of our findings, it may be thought that intoxication is correlated with the decreased SChE activity together with clinical findings. However, recent report has implied that the degree of plasma ChE inhibition is considerably different in patients poisoned by dimethoate and chlorpyrifos. Also, clinic features and prognosis vary according to their blood concentration [19]. Therefore, cholinesterase activity on admission must be interpreted carefully with respect to the amount of chemical exposure and type of OPs. Actually, it can be used to predict need for emergency intervention when the organophosphate ingested is known and its diagnostic value for that organophosphate has been studied.

Several case reports demonstrated that acute OPP may induce failure or damage in multiple organs such as renal impairment, pancreatitis, liver injury, respiratory distress syndrome, CNS depression and the others due to toxicity of OPs. In addition, failure of various organs may result in the death of acutely poisoned patients [7,9-12,21,24]. Moreover, clinical findings can be typical of multiple organ dysfunction syndromes [7,10].

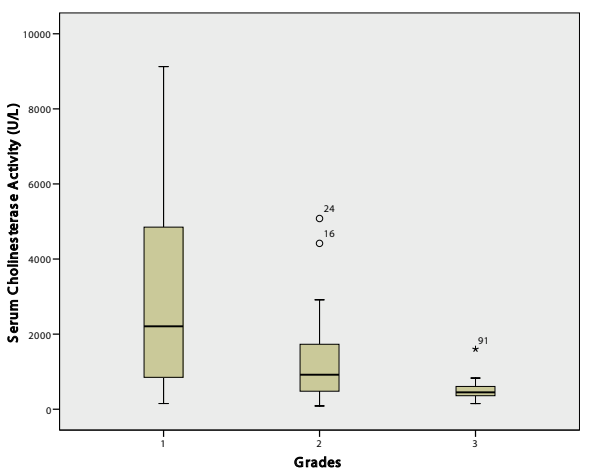

Figure 1. Serum cholinesterase activity according to grades
°, ∗ : observations with extreme values

For instance, acute renal failure in one patient with suicidal OPP occurred at the time of admission [10]. The value of SChE and creatinine was measured very low and too high on admission in this patient, respectively. In our study, the clinical signs, SChE and creatinine values associated with acute intoxication were similar to above patient on first day admission. Some studies have been indicated to renal injury, proximal renal tubular damage, rhabdomyolysis, and abnormal kidney function tests in severe OPP in rats [11,12]. As a result of these findings, acute renal failure was diagnosed on second and third day admission along with the evaluation of advanced kidney function in two patients of the grade 2 and four patients of the grade 3.

Previous studies have suggested that acute pancreatitis may develop following oral ingestion of several organophosphates [9,22]. A prospective study was reported by Singh et al. to find the incidence of hyperamylasemia and acute pancreatitis in patients with OPP. This report has indicated that mild elevation of serum amylase is common in patients with OPP [23], however; hyperamylasemia is reported in cases of severe OP and acute pancreatitis is less frequently [20,23]. Hsiao et al. and Harputluoglu et al. have reported to acute pancreatitis on admission after an attempted suicide by the ingestion of excessive organophosphate in human. In these reports, leukocyte count and serum amylase levels were very high measured when compared to reference range [9,22]. Similarly, in the present study, as cited above, these parameters were considerably high in patients of grade 2 and 3. Furthermore, acute pancreatitis was appeared on following days in three patients of these grades. Acute pancreatitis is a well known complication of OPP, whose pathogenic mechanism may be excess cholinergic stimulation within the pancreas and ductular hypertension [25]. Physicians should consider the possibility of acute pancreatitis in organophosphate intoxication if hyperamylasemia and hyperglycemia is found on laboratory screening. In spite of hyperamylasemia and hyperglycemia with presumptive pancreatic damage have been reported in the literature, there are no large prospective studies to address injury and imaging of pancreas [9,23,25].

Counter-regulatory hormone (catecholamine, cortisol) levels increase excessively in patients with acute OPP [20,24,25]. Persistent elevation of a counter regulatory hormone can reduce a person's sensitivity to insulin, whereas insulin accelerates glucose uptake and utilization in peripheral tissues (muscle, adipose). In addition, excessive adrenergic influences on metabolism cause glycogenolysis with hyperglycemia in OPP [20]. In our study, we determined higher glucose levels in patients of grade 1 but much more grade 2 and 3 compared to reference range. As a result of these findings along with above explanations, glucose concentration in blood can increase in response to acute-phase in poisoned patients with OPs. The toxic hazards of large organophosphate intake are that it could induce hyperglycemia, glucose

intolerance, and inhibition of insulin secretion as well.
The other associated abnormalities were polymorphonuclear leukocytosis (>11.000/ μL) on admission in all grades that had raised amylase, glucose, and depressed SChE in patients with acute OPP attempted to suicide. Increased sympathetic activity usually precipitates demargination, resulting in leukocytosis [20]. In addition to this, leukocytosis is a common finding in OPP [8,23]. Interestingly, our findings shows that the leukocyte counts according to normal levels arise obviously in parallel to the development of clinical signs from gradel to grade 3. WBCs in blood were measured significantly higher by 55.9 % in the grade 2 and 85.7 % in the grade 3 than in the grade 1. So, it may be a prognostic marker in acute OPP in association with intoxication. The alteration of leukocyte counts can be explained by the simultaneous occurrence of cholinergic stimulation along with an acute inflammation likely due to poisoning.
Elevations in hepatic enzymes can occur following the acute OPP [20]. Experimentally previous studies have demonstrated the abnormal liver function tests, hepatic necrosis, liver necrosis of mid-zonal type and fatty change in OP induced by fenthion and diazinon [11,12]. In the present study, transaminases were not increased excessively high when compared to reference.
In conclusion, the present retrospective study demonstrates that SChE activity depresses significantly in all grades and it is related to severity of organophosphate intoxication. Acute OPP in suicidal cases is associated with leukocytosis, hyperamylasemia and hyperglycemia.

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