Prognostic Value of Serum Cholinesterase in Organophosphate Poisoning*

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Objective: To determine whether serum cholinesterase level has a prognostic value in human acute organophosphorus poisoning.

Design: Cohort (prospective) prognosis study.

Setting: Medical ICU at University Hospital.

Patients: Thirty consecutive patients admitted to the ICU for acute organophosphate poisoning.

Measurements: Serum cholinesterase level was measured in all patients at the time of hospital admission. Severity of intoxication was assessed by the total dose of atropine required to relieve poisoning manifestations, the Simplified Acute Physiology Score, the need for assisted ventilation, and by a specific grading system previously validated that identified two groups of patients: group 1 (low severity, n=18) and group 2 (high severity, n=12).

Results: Serum cholinesterase level did not correlate with the total dose of atropine or with the Simplified Acute Physiology Score. Mean serum cholinesterase level was not significantly different between group 1 and group 2 patients (448 ± 400 U/L in group 1 compared with 611 ± 575 U/L in group 2 (p=NS); it was also not significantly different between patients with and without mechanical ventilation support (507 ± 371 vs 470 ± 409, respectively).

Conclusion: Serum cholinesterase levels have no prognostic value in acute organophosphate poisoning. Thus, a grading system to identify high-risk patients based on this measurement is most likely unreliable.

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ICU=intensive care unit; OP=organophosphate; OPP=organophosphate poisoning; SAPS=simplified acute physiology score

Key words: acute organophosphate poisoning; atropine; mechanical ventilation; prognosis; serum cholinesterase; severity index; simplified acute physiology score

Inadvertent or suicidal organophosphate poisoning (OPP) represents a serious problem in Tunisia and other developing countries because of the extensive use of these chemical compounds and their large availability in drug stores.1,2 As organophosphates (OPs) act as irreversible cholinesterase inhibitors, symptoms of OPP are related to the subsequent accumulation of acetylcholine, which is usually called a cholinergic crisis.3,4 Signs of OP insecticide poisoning may be classified into effects secondary to muscarinic, nicotinic, and central nervous system receptor overstimulation. Muscarinic overstimulation is manifested as hyperactivity of the parasympathetic system, including miosis, bradycardia, and hypersecretion of the salivary, lacrimal, digestive, and bronchial glands. Nicotinic effects include muscle fasciculations, cramping, and weakness while respiratory depression, seizures, and unconsciousness are the consequence of central nervous system toxicity. Mortality due to acute OP intoxication varies between 10 and 20 percent,5,6 generally due to respiratory failure.4,7 Objective, severity classification systems designed for use in clinical decision-making for OP-poisoned patients are scarce. In 1971, Namba and coworkers4 proposed the first grading of severity in acute OPP which is partly based on serum cholinesterase level. Although this score has never been validated, it continues to be used as an indicator of severity in OPP. Moreover, correlation between plasma cholinesterase activity and the severity of OPP has not been well established.8,9 The objective of this study is to determine whether serum cholinesterase level is a valid marker of severity in patients with acute OPP.

METHODS

Patients

Thirty patients with acute OPP admitted to our eight-bed intensive care unit (ICU) from November 1989 to November 1992 were prospectively enrolled in this study. The diagnosis of OPP was based on the following criteria: a history of intake or exposure to organophorus insecticide, clinical manifestations of OPP, and low serum cholinesterase level. Exclusion criteria included carbamate poisoning or severe pre-existing chronic health status. Age, sex, chronic health status according to Knau et al10 classification, type of OP ingested, initial serum cholinesterase level, severity of intoxication at presentation, and outcome were recorded for each patient. As the study involved no change in routine patient care, our Institutional Review Board waived the need for informed consent.

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Management of Intoxication

In addition to general and supportive measures, all patients were treated with gastric lavage and activated charcoal (100 g once) via nasogastric tube. The patients also received intravenous infusion of atropine to counteract bronchial hypersecretion and bradycardia. Oximes were not administered, although they had been given to nine patients prior to ICU admission.

Data Collection and Analysis

Serum cholinesterase activity was measured by spectrophotometry in all patients at the time of ICU admission. The normal value for serum cholinesterase activity in our laboratory ranged from 3,500 to 8,500 U/L. Severity of intoxication was then assessed according to each of the following processes. First, severity was evaluated by a grading system previously validated by Bardin and Van eeden.5 This grading is based on specific clinical findings pertaining mainly to the respiratory and central nervous systems and on the results of procedures such as chest radiographs and blood gas values. The revised form of this grading system categorized poisoning into three groups: mild, severe, and life-threatening poisoning. For the purpose of the current study, we combined mild and severe poisoning grades (mild-severe poisoning patients: group 1, n=18). The remaining patients formed the second group (life-threatening poisoning patients: group 2, n=12). Second, severity of intoxication was also assessed by the simplified acute physiology score (SAPS),1;1 the amount of atropine required to maintain its full effects (mydriasis, tachycardia, flushing, xerostomia, anhydrosis), and by the need for mechanical ventilation.

Comparison of cholinesterase level was performed between group 1 and group 2 patients and between mechanically ventilated and nonmechanically ventilated patients. Correlations were sought between serum cholinesterase activity and the other selected parameters of severity, namely SAPS and the dose of atropine required.

Statistical Analysis

Relationships between initial serum cholinesterase level and severity parameters were studied by simple linear regression. Student’s t test was used to compare the mean values (±SD) of serum cholinesterase between group 1 and group 2 and between mechanically ventilated patients vs patients without mechanical ventilatory support. Findings were considered significant at p<0.05.

Results

Thirty patients with the diagnosis of acute OPP have been enrolled in the study. Their clinical characteristics are summarized in Table 1. The type of organophosphorus was not identified in only six patients in whom the diagnosis of OPP was established on the decrease of serum cholinesterase activity, a history of exposure, and the presence of characteristic clinical manifestations. There were seven kinds of organophosphate compounds involved in the poisoning of our patients. The most common ones were mevinphos, dichlorvos, and parathion. Mean time interval between intoxication and ICU admission was 2.5 h (range, 30 min to 15.5 h). The initial clinical presentation in our patients is shown in Table 2. Muscarinic syndrome was present in more than 75 percent of cases (23 patients). Miosis and bronchial hypersecretion were the most frequent symptoms. Nicotinic symptoms were less frequently observed (5 patients) and seizures were noted in 11 patients.

The mean total dose of atropine given was 16.5 mg (range, 0 to 348 mg). Seven patients did not receive atropine because symptoms of muscarinic effects were absent in the initial presentation. Endotracheal intubation and ventilatory support was required in 12 patients. Three patients died within 48 h of ICU admission. The cause of death was ventricular fibrillation in one patient and high grade of atrioventricular block in the two others. No major electrolyte imbalance or hypoxemia was noted at the time of death. Serum cholinesterase activity in these patients were quite variable: 1,800, 300, and 100 U/L.

The difference in mean serum cholinesterase between group 2 (life-threatening poisoning) and group 1 (mild and severe poisoning) was not statistically significant. However, mean serum cholinesterase activity was less decreased in group 2 (611 ± 575 U/L vs 448 ± 409 U/L). Comparison of serum cholinesterase level in mechanically ventilated and nonmechanically ventilated patients did not reveal any significant difference (565 ± 571 vs 470 ± 409 U/L, respectively). In addition, no correlation was
found between serum cholinesterase level and the total atropine requirement. Of interest, mean SAPS was significantly higher in group 2 than in group 1 patients (12.2 ± 5 vs 3.5 ± 3.4, respectively, p < 0.001). However, no correlation was found between SAPS and serum cholinesterase activity.

**DISCUSSION**

The current study showed that in acute OPP, serum cholinesterase level measured at the time of ICU admission does not correlate with the clinical severity of poisoning. These findings could hardly be ascribed to the variable time between organophosphate exposure and the blood sampling for cholinesterase measurement. In most of our patients, this interval was less than 24 h, a period of time during which inhibition of serum cholinesterase activity reaches its maximum.3,4

It is believed that the toxicologic effects of OP are primarily, if not entirely, due to inhibition of acetylcholinesterase and to the subsequent accumulation of acetylcholine at the cholinergic synapses. Serum level of this enzyme is taken into account in the original grading of severity of OPP proposed by Namba and coworkers.4 Indeed these authors categorized patients into four groups, with latent, mild, moderate, and serious poisoning, on the basis of clinical findings and the serum cholinesterase level. However, to our knowledge, this classification has never been validated. Moreover, most of the studies suggesting the relationship between serum cholinesterase level and severity of acute OPP were based on some case reports.12-15 The largest study dealing with the prognostic significance of cholinesterase level was conducted in 107 patients by Tsao et al6 who found that respiratory failure developed almost exclusively in patients classified as having moderately severe or severe poisoning on the basis of the decrease of serum cholinesterase activity. They also found that survival was significantly higher in patients who exhibited a very mild decrease of this enzyme. However, the results of this study were seriously hampered by the heterogeneous enrollment criteria, since 13 patients had acute carbamate poisoning and 14 had either an association of carbamate and OP poisoning or an uncertain agent. Since some carbamate compounds may act as cholinesterase inhibitors, they may represent a confounding factor in the interpretation of the clinical course in this group of patients.16

Correlation between serum cholinesterase level and death rate is probably more interesting than any other severity grading. However, only three deaths occurred in our study making it impossible to use this criterion. Therefore, we elected to correlate serum cholinesterase level with indices of severity that do not include serum cholinesterase activity such as the scale of Bardin et al5,8 and SAPS. The scale of Bardin et al5,8 is a specific grading system previously validated in patient victims of OPP. However, SAPS is a reliable general index used for a large range of patients in the ICU.11 This scoring system showed that the degree of physiologic derangement correlates closely with the outcome in overall critically ill patients and even for relatively small groups of patients within specific disease categories such as acute pancreatitis and cardiogenic shock.17,18 In the present study, we showed the reliability of this score to stratify patients with acute OPP prognostically since we found a significantly higher SAPS in group 2 than in group 1 patients according to the severity grading system of Bardin et al.5,8 To the best of our knowledge, this is the first study that validates SAPS11 as an indicator of severity in acute OPP.

The amount of atropine required to maintain its full effects is often used to reflect the severity of OPP.2,6 In our study, atropine requirement did not correlate with serum cholinesterase level. One explanation to these findings is that atropine is only a muscarinic receptor antagonist whereas cholinergic crisis symptoms are relevant to overstimulation at variable degree of both muscarinic and nicotinic receptors.1 Consequently, atropine was required only when muscarinic symptoms were present. Indeed, seven of our patients (four patients in group 1 and three in group 2) did not receive atropine. In these patients, the diagnosis of OPP was based on a positive history of intake or exposure and low serum cholinesterase level.

The need for assisted ventilation is usually considered as an indicator of illness severity in patients with acute OPP.6 However, we were unable to find any statistically significant difference in mean serum cholinesterase levels between mechanically ventilated patients and patients who did not require mechanical ventilation.

Although numerous experimental studies have reported the lack of relationship between cholinesterase activity and clinical severity,19,20 clinical data supporting these findings are limited.5,21 Our study confirmed that serum cholinesterase level is not reliable to assess the clinical severity of acute OPP. Some explanations for these findings could be proposed. First, tissue concentration of cholinesterase (true cholinesterase), which is thought to be more closely related to clinical manifestations of poisoning, is poorly correlated with plasma level of the enzyme (pseudo-cholinesterase).5 The respective sensitivity of these two enzyme species to OP inhibition is probably different. Second, it seems possible that a direct OP toxic reaction independent of cholinergic mediation may occur; this hypothesis was previously postulated to explain some aspects of the cardiac disorders seen in...
patients with acute OPP. 22

In summary, no correlation between serum cholinesterase level and the severity of OPP was found in this study. A grading system to identify high-risk cases in OPP based on the plasma level of this enzyme is therefore not reliable. Cholinesterase level should be considered no more than a marker of OP intoxication and does not involve any prognostic implication.

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REFERENCES