ORIGINAL ARTICLE

Serum Paraoxonase 1 Activity in Patients with Organophosphate Poisoning: A Potential Indicator of Prognosis

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Abstract

Background: Human serum paraoxonase 1 (PON1) hydrolyzes organophosphate (OP) compounds and so significantly alters an individual's susceptibility to the toxicity of these chemicals. The study was designed to assess the serum PON1 activity in a series of patients with OP poisoning.
Methods: Suspected OP poisoning patients presented within 6 hours of consumption at emergency department were recruited. Demographic information of patients, clinical findings, treatments given, complications, length of hospital stay and clinical outcome were collected into datasheets. Patients were graded into moderate and severe poisoning. Serum PON1 was measured by ELISA method and serum cholinesterase by butyrylthiocholine method.
Results: Mean serum PON1 level in patients with severe poisoning was significantly lower than those with moderate poisoning (426 ± 179 U/L vs. 868 ± 79 U/L, $P < 0.001$). Serum PON1 significantly correlated with serum cholinesterase levels ($r = 0.400$, $P < 0.001$) and negatively associated with total length of hospital stay ($r = -0.338$, $P < 0.001$), total atropine dose ($r = -0.826$, $P < 0.001$), serum amylase ($r = -0.331$, $P < 0.001$), lipase ($r = 0.260$, $P = 0.011$) and total creatinine kinase ($r = -0.456$, $P < 0.001$). Serum PON1 and cholinesterase levels were significantly lower in expired patients and those who required ventilation assistance as compared to recovered patients who did not require ventilation assistance.
Conclusion: Lower PON1 activity was significantly associated with lower serum cholinesterase and poorer outcomes. PON1 activity may be considered as an indicator of prognosis in OP poisoning.

Keywords: Cholinesterase; Organophosphate Poisoning; Pesticides; Paraoxonase 1

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INTRODUCTION

Pesticides are synthetic chemicals used for controlling the domestic and agricultural pests including insects, plant pathogens, weeds and mollusk. Although there are obvious benefits from the use of pesticides, there are also certain drawbacks. Pesticide poisoning is a serious health problem in many countries including India (1,2). World Health Organization estimated that three million pesticide poisoning episodes occur annually worldwide, and out of which around 300,000 die (3,4). According to a nationally representative mortality survey, around 187,000 suicide deaths occur annually in India, in which in 38.8% pesticide ingestion is the method of suicide (5).

The most common pesticides used for poisoning are organophosphates (OPs). OP poisoning is an important medical emergency in the developing countries like India, where the agriculture is an important profession (6). Hospital mortality rate of OP poisoned patients is reported to be as high as 15-20% in India (7-10). OP poisoning causes the most common suicide-related deaths in Southern and Central India (11,12). Commonly used OPs are acephate, anilophos, chlorpyrifos, diazinon and dimethoate (13,14). The mode of action of OP pesticides is through the inhibition of acetyl cholinesterase and butyryl cholinesterase (BChE; also known as serum cholinesterase) which are both responsible for hydrolysis of acetylcholine, an essential neurotransmitter at nerve endings (3). Inhibition of these enzymes causes the accumulation of acetylcholine at the synapses which thereby continuous stimulation of receptors occurs. Symptoms are classified into muscarinic, nicotinic and central depending on the actions over the respective receptors (3,15,16).

Paraoxonase 1 (PON1), an antioxidant enzyme, catalyzes the hydrolysis of OP compounds and nerve gases. By metabolizing OPs, PON1 significantly diminishes toxicity of these poisons in an individual (17). PON1 activity of an

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individual can vary to a large extent. It is reported that PON1 levels can vary by at least 13-fold and the activity up to 40-fold (4). *PON1* gene exhibits single nucleotide polymorphisms (SNPs) in the coding (192Q/R and 55LM) region of the gene (18). Type A of PON1 (presently known as Q isozyme, Glutamine at position 192) can remarkably be less proficient than type B (presently known as R isozyme, Arginine at position 192) in hydrolyzing paraoxon. Then again, diazoxon, soman and sarin break down when exposed to water – the procedure carried out through the Q is obviously preferred to that of the R-isozyme (19). A second polymorphism at position 55, including a leucine → methionine substitution, influences the PON1 function in a less extent compared with that of polymorphism at position 192. The polymorphic circulation of PON1 indicates extraordinary interethnic fluctuation. The recurrence of gene for PON1 R192 allele is 0.31 in Caucasian populace, 0.41 in Hispanic populaces, 0.66 in a Japanese populace and 0.31 in Turkish populace (17). Due to inter-individual difference of *PON1*, evaluation of PON1 activity in OP poisoned patients would be useful in: (1) determining the severity of poisoning, (2) predicting patient's ability to detoxify OP compounds, and (3) understanding the prognostic utility of PON1. Therefore, this study was designed to assess the serum PON1 activity in patients with OP poisoning. The main objectives of the study were to analyze serum PON1 and cholinesterase activities, the severity of OP poisoning based on clinical signs and symptoms and to study the association between serum PON1 activity, biochemical investigations, severity and clinical outcome in a series of OP poisoned patients.

METHODS

Study setting and subjects

This was a prospective cross-sectional study conducted in Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) hospital, after obtaining the approval from Institute Research Council and Institute Human Ethics Committee (Ethical code: JIP/IEC/2016/1004). Written informed consent was taken from study subjects or their legal guardians prior to recruitment. All adults suspected OP poisoning cases (> 18 years old), who presented within 6 hours after consumption of the poison at Emergency Department were recruited in the study based on history and clinical examination. The severity of OP poisoning was assessed based on the classification proposed by Proudfoot depending on signs and symptoms (20,21). Patients with multiple pesticide poisoning, concurrent poisoning with other drugs and medicines (e.g. opioids, diazepam, barbiturate, etc.), chronic medical illness, pregnancy and being under long-term treatment with medicines with the potential of affecting neurological functions (aminophylline, succinylcholine, reserpine, and phenothiazine-type tranquilizers) were excluded from study.

Data Collection

Patients with the history of OP pesticides consumption were first being examined for any hemodynamic compromise, resuscitation was carried out and gastric lavage was given. Under the strict aseptic condition, five milliliter venous blood was collected from the subjects enrolled in the study before antidote therapy (6 hours after OP ingestion on average). Blood was centrifuged, half of the serum separated was used for routine biochemistry investigations and the remaining half was stored at -70^{oC} to be used later for PON1 analysis. The detailed demographic, clinical data, course of illness in the hospital including total dose of atropine required, complications, supportive therapy like ventilator assistance, the length of hospital stay and clinical outcome (death and ventilation assistance requirement or recovery and no ventilation assistance requirement) were recorded in datasheets. The routine blood parameters such as glucose, blood urea nitrogen (BUN), creatinine, bilirubin, aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), amylase, lipase and creatine kinase-total (CK-T) were measured using an autoanalyzer (Beckman AU680, Brea, CA, USA). Cholinesterase activity (BChE level) was measured using butyrylthiocholine method (BioSystems S.A., Barcelona, Spain) with a detection limit of > 123 U/L. The intra-assay and inter-assay coefficients of variation were 1.0% and 1.0%, respectively. Serum PON1 levels were measured using a commercially available enzyme-linked immunosorbent assay kit (Ray Biotech Life, Peachtree Corners, GA, USA) according to the manufacturer's protocol. Detection limit was > 31.2 U/L. The intra-assay and inter-assay coefficients of variation were 5.1% and 5.7%, respectively.

Statistical analyses

The data were analyzed using SPSS software, version 19.0 (IBM SPSS, Armonk, NY, USA). The distributions of categorical data such as gender, socio-demographic status, ventilator support requirement and final outcome (death, recovery) are expressed as frequency and percentage. The continuous data such as age, dose of administered atropine, length of hospital stay are expressed as mean (± standard deviation) or median (range), whichever was appropriate based on the normality of data distribution. The comparison of serum PON1, BChE level, demographic factors, clinical variables, total dose of antidote required and outcome measures (death and assisted ventilation requirement) between two groups were done using Student's t-test or Mann-Whitney U test, whichever was appropriate based on the normality of data distribution. Chi-squared test was used to compare qualitative variables between 2 groups. Multiple logistic regression analysis was done to investigate the association between serum PON1, cholinesterase, CK-T, lipase and amylase levels with prognosis in OP poisoning patients. P values less than 0.05 were considered as statistically significant.

RESULTS

Ninety patients with OP poisoning attending emergency department from Jan 2017 to Dec 2017 were recruited in the study. The majority of subjects were men (n = 62, 68.9%). Based on poisoning severity grading, 46 patients had moderate poisoning (i.e. defined by presence of fatigue, headache, paresthesia, nausea and vomiting, miosis, diaphoresis, salivation, abdominal pain, diarrhea, being able to ambulate, general weakness, dysarthria and regional

fasciculation) and 44 patients had severe poisoning (i.e. defined by presence of generalized fasciculation, absent pupillary reaction, flaccid paralysis, pulmonary crepitation, respiratory distress, cyanosis, unconsciousness, inability to ambulate). There were no statistical significance differences with respect to age, gender distribution, pulse rate, plasma O_2 saturation and systolic blood pressure between severe and moderate poisoning. Mean diastolic blood pressure in severely poisoned patients was significantly lower than moderate ones. In patients with severe poisoning, ventilatory support requirement and death rate were significantly higher compared with those of moderate poisoning. The median (range) length of hospital stay was significantly higher in severely poisoned patients compared with moderately poisoned one. The patients were treated with doubling dose regimen of atropine until signs of atropinization appear (heart rate >100 bpm, decreased bronchorrhea, dilatation of pupil) and then, 10-20% of the loading dose has been used for maintenance. Mean total atropine dose required for severe poisoning was significantly higher than moderate poisoning (Table 1). Oximes have not been given to the patients.

Blood glucose, total bilirubin, AST, ALT, ALP, BUN and creatinine were not statistically significantly different between severe and moderate poisoning cases. Mean serum amylase, CK-T and lipase levels were significantly higher in severely poisoned patient compared with moderately poisoned ones (Table 2). Patients with severe OP poisoning had significantly lower PON1 levels compared with moderately

Table 1. Demographics, clinical characteristics and outcome of the study subjects

Parameters	Severe poisoning	Moderate poisoning	P value
Number of patients	44	46	
Age (years); mean ± SD	45 ± 14	36 ±17	0.203
Gender (Male: Female); n (%)	32 (72.7): 12 (27.3)	30 (65.2): 16 (34.8)	0.442
Length of hospital stay (Days); median (range)	7.1 (4.2-11.6)	4.2 (2.5-5.7)	0.020
Required atropine dose (mg), mean ± SD	172 ± 15	63 ± 8	< 0.001
Pulse rate (beat/min); mean ± SD	92.6 ± 9.7	94.9 ± 9.5	0.889
O_2 saturation (%); mean ± SD	95 ± 3	95 ± 4	0.060
Systolic blood pressure (mm Hg); mean ± SD	117 ± 15	116 ± 12	0.141
Diastolic blood pressure (mm Hg); mean ± SD	69 ± 9	82 ± 13	0.017
Ventilation assistance; n (%)	16 (36.4)	0 (0)	< 0.001
Outcome, n (%)			
Death	8 (18.2)	0 (0)	0.002
Recovery	33 (75)	45 (97.8)	
Leaving hospital against medical advice	3 (6.8)	1 (2.2)	

Table 2. Biochemical laboratory investigations of the study subjects

Parameters	Reference range	Severe poisoning	Moderate poisoning	P value
Number of patients		44	46	
Serum cholinesterase (U/L); mean ± SD		1362 ± 201	3059 ± 1817	< 0.001
Serum paraoxonase I (U/L), mean ± SD		426 ± 179	868 ± 79	< 0.001
Blood glucose (mmol/L); mean ± SD	3.9-7.8	6.6 ± 1.0	6.5 ± 1.1	0.532
Total bilirubin (µmol/L); mean ± SD	6.8-20.5	16.6 ± 6.0	15.9 ± 7.5	0.144
AST (U/L); mean ± SD	0-40	56 ± 11	55 ± 11	0.998
ALT (U/L); mean ± SD	0-45	31 ± 15	25 ± 12	0.142
ALP (U/L); mean ± SD	30-125	141 ± 21	142 ± 24	0.381
Serum amylase (U/L); mean ± SD	28-140	170 ± 90	139 ± 47	< 0.001
Serum lipase (U/L); mean ± SD	0-60	81 ± 44	64 ± 25	< 0.001
Creatine kinase-total (U/L); mean ± SD	24-195	251 ± 88	160 ± 27	< 0.001
Blood urea nitrogen (mmol/L); mean ± SD	2.5-6.7	4.3 ± 1.6	4.5 ± 1.4	0.378
Creatinine (µmol/L); mean ± SD	53.0-106.0	80.4 ± 13.3	86.6 ± 12.4	0.642

poisoned patients (426 ± 179 U/L vs. 868 ± 79 U/L; P < 0.001). In addition, mean BChE level of severely poisoned patients was significantly lower compared with moderately poisoned ones (Table 2).

Bivariate correlation analyses showed that serum PON1 concentration was positively associated with serum BChE levels (r = 0.400, P < 0.001) and negatively associated with length of hospital stay (r = - 0.338, P < 0.001), total atropine dose (r = - 0.826, P < 0.001), serum amylase (r = -0.331, P < 0.001), lipase and CK-T (r = -0.456, P < 0.001). Comparing expired patients and those who required ventilation assistance with recovered patients who did not require ventilation assistance, serum PON1 and BChE levels were significantly lower and the required atropine dose, serum amylase, lipase and CK-T (Table 3).

To evaluate the effect of serum PON1, BChE, amylase, lipase and CK-T on the prognosis of OP poisoning, multivariate regression (binary logistics) analysis was used. It was found that low serum PON1 and cholinesterase levels and high serum amylase, lipase and CK-T levels were associated with poor prognosis (death and ventilation assistance requirement) (Table 4).

DISCUSSION

Suicidal ingestion of OP pesticides has been rising in the past two decades due to easy availability of these poisons, stressful lifestyle and jobs, loneliness, emotional liability and many other socioeconomical factors (22). Although severity of poisoning depends on amount and toxicity of the pesticide as well as route of exposure, patient's intrinsic characteristics such as genotype might be a contributory factor for severity of poisoning. PON1 is an enzyme involved in the detoxification of several important OP pesticides (23,24). PON1 phenotype or genotype have been varied among population and might have effect on severity of OP poisoning. In this study, we found that PON1 activity is significantly diminished in severely OP poisoned patients. In addition, serum PON1 levels were significantly correlated with serum cholinesterase levels. Richard et al similarly showed low PON1 activity in severe OP poisoning and ascertained positive correlation with serum cholinesterase levels (11). Moreover, Akgur et al found positive correlation between acetylcholinesterase and PON1 activities in a study on 18 agricultural male workers who were exposed to OP poisoning in Turkey (16). Hofmann et al also showed significant association of PON1 activity and BChE levels (25).

Our patients with severe OP poisoning experienced greater inhibition of cholinesterase, which led to development of muscarinic effects. Hence, higher atropine dose was required to treat muscarinic effects for severely OP poisoned patients as compared to moderately poisoned ones. Furthermore, patients with severe poisoning had higher incidence of respiratory complications and required ventilation assistance in a higher extent as compared to moderate poisoning. Kumar et al likewise showed high incidence of assisted ventilation requirement in severe OP poisoning and suggested the use of serial serum cholinesterase analysis to assess prognosis of ventilation (17). In fact, more complications and greater dependence to ventilation assistance in patients with severe OP poisoning increased total length of hospital stay as observed in the present study.

In this study, there was a male predominance in the OP

Table 3. Comparison of study variables between patients with poor and favorable outcomes

Parameter	Death + ventilation assistance requirement	Recovery + no ventilation assistance requirement	P value
Number of patients	24	63	
Serum cholinesterase (U/L); mean ± SD	580 ± 166	2385 ± 253	0.027
Serum paraoxonase I (U/L), mean ± SD	357 ± 49	672 ± 100	< 0.001
Serum amylase (U/L); mean ± SD	198 ± 96	129 ± 47	< 0.001
Serum lipase (U/L); mean ± SD	112 ± 19	54 ± 32	0.007
Creatine kinase-total (U/L); mean ± SD	224 ± 86	106 ± 58	0.014
Required atropine dose (mg), mean ± SD	180 ± 13	54 ± 23	0.003

Table 4. Multivariate regression (Binary Logistics) analyses in all subjects

Independent variables	Beta coefficient	Adjusted Odd ratio (95% confidence interval)	P value
Serum cholinesterase	- 0.126	4.45 (1.42-9.54)	< 0.001
Serum paraoxonase I	- 0.427	5.53 (1.12-10.65)	< 0.001
Serum lipase	0.125	2.88 (1.10-4.66)	0.026
Serum amylase	0.159	3.17 (1.25-5.58)	0.013
Creatine kinase-total	0.104	2.92 (1.12-4.72)	0.024

poisoned patients that was in agreement with several other studies (8,9,26,27). Shivaramu et al attributed this gender deviation in OP poisoning patients to change in the lifestyle, psychological and financial problems that have majorly affected men during the recent decades (14). In the present study, serum amylase and lipase levels were significantly higher in patients with severe OP poisoning as compared to moderate poisoning and were correlated negatively with serum PON1 levels. Hyperamylasemia, which is often noted following OP poisoning, may be due to the fact that acute pancreatitis results from excessive cholinergic stimulation of pancreas by OP compounds (28). In agreement with our findings, Lin et al demonstrated that mean amylase level was elevated in severely OP poisoned patients requiring respiratory support and additionally serum amylase levels was ascertained as a predicting factor of ventilator support requirement in OP poisoning (29). In a prospective study by Singh et al, amylase was elevated in 48.95% in patient with severe fenthion poisoning and serum amylase showed persistent elevation during serial measurements (30).

Serum CK-T was significantly higher in our patients with severe OP poisoning as compared to moderate poisoning and was correlated negatively with serum PON1 levels. Muscular injury is a common finding in OP poisoning patients which leads to increased CK-T levels. Sen et al similarly established a strong positive correlation between serum CK-T and the severity of OP poisoning and that serum CK-T can be used as a predictor of outcome in OP poisoning (3). Hassan et al also ascertained correlation between initial CK-T levels and severity of OP poisoning (31). Correspondingly, Battacharya et al demonstrated that CK-T can be elevated in severe OP poisoning even in the absence of intermediate syndrome (32).

In this study, higher mortality rate was observed in patients with severe OP poisoning compared to moderate cases. Serum PON1 and cholinesterase levels in recovered patients who did not require ventilatory support was significantly higher than deceased patients and those who required ventilation. Prasad et al similarly ascertained lower serum cholinesterase levels in deceased OP poisoned patients compared with survived ones (21). Low PON1 activity in patients with OP poisoning leads to less clearance of pesticides from systemic circulation (23). Hence, greater inhibition of cholinesterase and profound muscarinic and nicotinic actions of acetylcholine occur, which predisposes OP poisoned patient to more serious complications such as respiratory compromise, muscular injury and acute pancreatitis. Although this work proved that lower PON1 activity is associated with increased severity of OP poisoning, poorer clinical outcome and higher mortality rate, whether serum PON1 offers any greater advantage over serum cholinesterase for predicting severity and prognosis of OP poisoning is yet to be clarified in future studies.

LIMITATIONS

concentrations of the ingested OP pesticides were not evaluated in the present study. In fact the diagnosis of OP poisoning was confirmed by patients' history, clinical findings and response to antidote treatment. Hence, the correlation of serum OP compounds concentrations and PON1 activity cannot be determined. Moreover, greater severity of OP poisoning due to higher serum OP compounds levels cannot be ruled out. Serial assessment of PON1 and cholinesterase was not conducted in this study and so the change of these blood indicators during the poisoning course and antidote treatment cannot be assessed. Genetic sequencing of *PON1* gene and PON1 RNA expression were not analyzed to determine whether lower PON1 activity was due to inhibition at DNA or RNA level or both in severe OP poisoning.

CONCLUSION

Serum PON1 activity was significantly lower in patients with severe OP poisoning as compared to patients with moderate poisoning. Lower PON1 activity was significantly associated with lower serum cholinesterase and poorer outcomes. PON1 activity may be considered as an indicator of prognosis in OP poisoning.

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