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Glycemic Status in Organophosphorus Poisoning

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ABSTRACT

Background: Organophosphorus(OP) poisoning, in addition to its cholinergic manifestations shows metabolic derangements leading to hyperglycemia. Apart from inhibiting acetylcholinesterase it also induces oxidative stress to exhibit this manifestation. The present study aims to assess the glycemic status of OP poisoned patients and its association with various factors in OP poisoning like oxidative stress and dose of atropine.

Methods: This is a prospective study which recruited 102 patients above 18 years of age with history of OP poisoning. They were categorized into 3 grades-mild, moderate and severe based on the Peradeniya Organophosphorus Poisining Scale. The routine biochemical parameters along with serum malondialdehyde (MDA) and cholinesterase were estimated in the study group.

Results: Hyperglycemia and glycosuria were observed, with majority cases of hyperglycemia (57%) noticed in the severe group. There was a rise in the random plasma glucose (RPG), serum malondialdehyde (MDA), total dose of atropine across the groups along with a fall in the serum cholinesterase with increase in severity of poisoning. The fall in plasma glucose at the time of discharge was significant in all three groups when compared to the admission random plasma glucose(RPG) level. This transient hyperglycemia exhibited a significant positive association with serum MDA and dose of atropine administered during treatment ($p<0.05$).

Conclusions: Glycemic status in OP poisoning may play a role in identifying the severity of poisoning at the time of admission.

Keywords: Atropine; hyperglycemia; organophosphorus; oxidative stress; random plasma glucose.

INTRODUCTION

Organophosphorus (OP) poisoning is a common accidental health hazard in the world.[1] Presently these heterogeneous compounds are the most commonly used suicidal poisons, particularly for young adults because of their easy availability. A history of acute exposure to an organophosphorus pesticide and development of characteristic cholinergic clinical effects[2]. It carries a serious accidental health hazard in India with a raised mortality rate that needs early hospitalization and corrective measures.[3]

The OP compounds bind to cholinesterase by covalent binding of phosphate radicals to active sites of cholinesterases making them enzymatically inert resulting in excess of acetylcholine and cholinergic effects in central nervous system, peripheral nervous system as well as skeletal myoneural junction.[4] OP poisoning is associated with increased lipid peroxidation and low glutathione level causing damage to cell membrane and DNA, resulting in cell death.[5-7] The protective effect of Vitamin E against oxidative stress has also been seen.[8]

In addition to the clinical features of increased cholinergic manifestations biochemical alterations like

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hypokalemia,[3] glycemic changes[9,10] are also noticed in these cases. Few animal studies have registered the increased cholinergic activities because of raised glucose level.[9] Others have shown hyperglycemic changes during the anticholinesterase poisoning.[10] In organophosphorus poisoning, glycosuria has been previously shown with or without hyperglycemia, though glycemia was noticed for transient period.[10-12] The metabolic linkage between pesticides exposures and diabetes in humans is also known,[13] with rare observation of OP poisoning presenting as diabetes ketoacidosis.[14,15] Though the cholinergic effect has adverse effects on pancreas, liver as well as lipid peroxidation, yet the glycemic alteration in OP poisoning and its relation with severity of poisoning needs further evaluation.

METHODS

The present study is a prospective observational study and was carried out in Shriram Chandra Bhanja Medical College, Cuttack. Patients over 18 years of age with a relevant history and clinical signs and symptoms with diagnosis of short term exposures of OP poisoning and biochemical observation of decreased serum cholinesterase activity below reference range were included in the study after getting verbal consent from patient's attendant. Out of 109 patients, 102 patients were enrolled in the study as death of seven patients took place after admission within the period of treatment. The study group were categorized according to their severity into three grades, mild, moderate and severe by the Peradeniya Organophosphorus Poisoning(POP Scale).[3,17] Five ml of blood along with a sample of urine was collected prior to start of treatment. A complete blood count along with random plasma glucose, renal function test, liver function test, serum cholinesterase, were performed along with HbA1c for exclusion of previous diabetic state, using Flexor XL Biochemistry Autoanalyzer. Plasma MDA was estimated by spectrophotometric measurement of thiobarbituric acid reactive substance[18]. Urine was tested for presence of sugar, albumin and ketone bodies using reagent strip for urine analysis (*Mission 3P*). Appropriate treatment of the patients was started along with atropine and pralidoxime. Atropine was given in the doses of 0.5 to 2mg atropine intravenously every 15 minutes till the signs of atropinisation appeared. Patients with history of poisoning with other toxic substances, undiagnosed toxicity, previous known diabetes mellitus, chronic renal disease, chronic pancreatic disease, chronic liver disease, alcoholics, OP poisoning for more than 24 hours prior to admission and pregnant ladies were excluded from this study.

The total dose of atropine needed for the complete recovery during treatment was calculated and noted down. On the day of discharge, random plasma glucose was again estimated to find out the glycemic status and urine was tested for presence of sugar. The observed glycaemic status was correlated with severity of toxicity, serum cholinesterase level, total dose of atropine needed for complete recovery. The glycemic status on the day of admission was compared with day of discharge. Random plasma glucose >140mg/dl was taken as hyperglycemia.[19]

Statistical analysis were performed using SPSS 21.0 version, describing discrete and continuous data. The results were expressed in mean and standard deviation. Anova test, Chi Square tests were used to get difference in various groups, with $p<0.05$ as significant. The study has got the institutional ethical clearance.

RESULTS

Amongst 102 patients, female subjects (n=60) were higher than males(n=42). Most of them (87%) were from a rural background, and belonged to the lower and lower middle socio-economic background. The mode of presentation was mostly cholinergic manifestations such as vomiting (82%), salivation (71%), sweating (46%), bradycardia (43%), altered sensorium (36%) and fasciculation (24%)(Fig-1). The age groups of 42% patients were within 21-40 years with a mean age of 28.05 ±5.3 years.

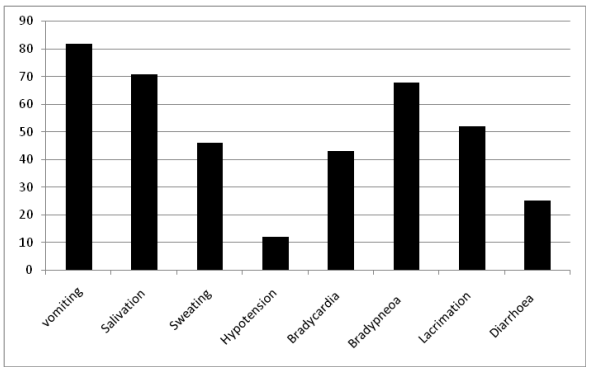

Figure 1. Clinical presentation(%) of patients

As per the POP score, 102 patients were subdivided into mild (n=50), moderate (n=33) and severe (n=19) grades. A total 28 patients having RPG >140 mg/dl. Majority of cases, ie. 57.8% had RPG in hyperglycaemic range i.e >140 mg/dl. In addition, 8(16%) and 9(27.2%) cases were observed to be hyperglycemic in mild and moderate groups respectively. Glycosuria was noticed only in 8 cases of OP poisoning (28.6 %), two in mild and two in

moderate groups and four in severe groups respectively, (Table-1). Albuminuria and ketonuria was not detected in any of them.

Table 1. Glycemic patterns at time of admission

Grade	Total no. of patients	Patients with hyperglycemia (%)	Patients with glycosuria (%)
1 (Mild)	50	8 (16 %)	2(4%)
2 (Moderate)	33	9 (27.2 %)	2 (6%)
3 (Severe)	19	11 (57.8%)	4(21.0%)
Total	102	28(27.4 %)	8(7.8 %)

The present study group comprised of non diabetic patients, revealed by HbA1C level of 5.5±0.2gm% at the time of admission. The mean random plasma glucose of the study population at the time of admission showed a value of 119.3± 33.7 mg/dl ranging between 67-211 mg/dl with 28(27.4 %) cases having RPG value above 140 mg/dl (Table-2).

Table 2. Biochemical parameters at the time of admission

Parameters	Mean ± S.D
RPG (mg/dl)	119.3±33.7
HbA1c (%)	5.5±0.2
Urea (mg/dl)	28.1± 9.0
Creatinine (mg/dl)	1.11±0.3
Bilirubin (mg/dl)	0.9±0.3
SGOT (IU/L)	47.2±18.1
SGPT(IU/L)	38.2±18.4
ALP(IU/L)	201.8 ± 68.6
Plasma MDA(nmol/ml)	51.7±6.1
Cholinesterase (IU/L)	2903.9±1803

The graded fall in serum cholinesterases with rise in POP score indicated an increase in severity of poisoning. The total dose of atropine required for recovery, i.e. till complete atropinisation also documented a graded increase dose along with the severity grades. Oxidant stress measured in terms of plama malondialdehyde also revealed a rise with clinical severity(Table-3). The fall in serum cholinesterase value was more pronounced in patients having RPG >140 mg% , parallel with severity in grade of poisoning. Total atropine dose was more for those patients having RPG >140 mg%, than those having RPG < 140mg%.

Table 3. Biochemical parameters with severity of poisoning

POP Score	No. of patients (%)	Serum Cholinesterase (IU/L)	RPG (mg/dl)	MDA (nmol/ml)	Total dose of Atropine (mg)	Total no. of days
0-3(mild)	50 (49.1%)	4049.6±2012.1*	108.3 ±28.2*	48.5 ±5.5	107.7± 19.2*	5.4 ±0.5
4-7 (moderate)	33 (32.3%)	2751.8±1604.7*	121.6 ±33.8*	54.5±6.4	144.9± 22.8*	5.9 ±0.4
8-11 (severe)	19 (18.6%)	1164.3±1004.7*	144.2 ±34.2*	55.7±6.7	180.1± 19.6*	6.8 ±0.4

*P value<0.05

The rise in RPG showed a significant positive association(p=0.003) with the total dosage requirement of atropine(Fig-2). The increase in mean RPG and dose of atropine, demonstrated inverse relation with graded fall in serum cholinesterase with severity of poisoning. Plasma malondialdehyde also registered a weak positive correlation (p<0.017) with admission RPG revealing a probable role of oxidant injury in metabolic manifestations of OP Poisoning. However MDA and RPG did not reveal significant relation with serum cholinesterase concentration.

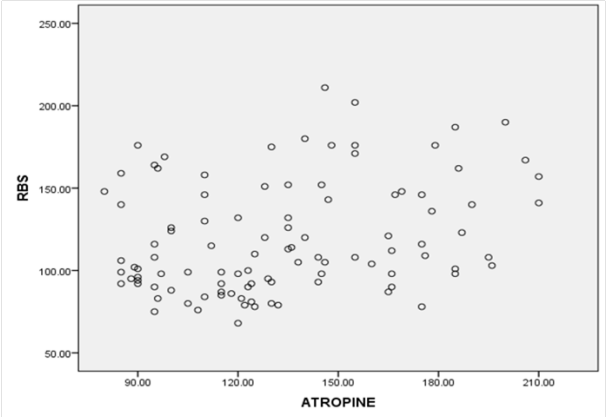

Figure2. Correlation graph of Random Plasma Glucose with Atropine

On the day of discharge, there was a significant fall (p<0.001), in the mean RPG value in all groups in comparison to the day of admission(Table-4). Glycosuria was absent on the day of discharge, except in one case, where the degree of glycosuria decreased, but not completely.

Table 4. Random plasma glucose at time of admission and discharge

POP Scale	RPG in mg/dl (on admission)	Final RPG in mg/dl (on date of discharge)
Mild (0-3)	108.3±28.2	94.3±23.8*

Moderate (4-7)	121.6±33.8	103.9±15.9*
Severe (8-11)	144.2 ±34.2	110.2±18.3*

* p<0.001

DISCUSSION

Organophosphorus poisoning has been diagnosed as a prime problem in developing countries like India because of its predominant use in pest control and crop protection. The diagnosis of OP poisoning is mainly based on the history of ingestion or exposure, clinical features, low serum cholinesterase levels and therapeutic response to atropine.[1,4]

The most affected group included females within the age group of 21-40 years. Similar demographic data was seen in the study conducted by others.[3] The clinical symptoms included classic cholinergic syndrome, vomiting and salivation being the major symptoms. Serum cholinesterase estimation revealed a decreasing trend with increased severity which is seen in other studies as well, highlighting the inhibition of cholinesterase with acetylcholine accumulation at the nerve synapses and neuromuscular junctions, with over-stimulation of acetylcholine receptors for manifestations of the disease.[5,6,9] The progressive rise in Serum MDA from Grade I to Grade III, reflected by increased lipid peroxidation in this study has also been cited by Mishra et al. and Vidyasagar et al.[6,7] Vidyasagar et al. in their study found an increased level of MDA in OP poisoned patients who failed to survive, reflecting increased lipid peroxidation, cell damage and death. Significant improvement was noticed in the AChE (serum and RBC) levels of patients with specific treatment but without much change in the antioxidant status as reflected by the superoxide dismutase and MDA levels.[8]

Liu et al. observed exacerbation of cholinergic manifestations of parathion by giving glucose load, where a role played by nitric oxide is suspected.[9] Besides cholinergic manifestations, effect on blood sugar is an observation of metabolic effect in OP poisoning.[10,11] Shoba et al. reported transient glycosuria in 69% of patients with OP poisoning. However, none of the patients developed new onset diabetes mellitus.[11] Others have suggested that the oxidant stress due to poisoning and the renal damage caused by this might have resulted in metabolic changes noticed.[5,6,12,13] Acute poisoning has also presented with diabetic ketoacidosis in some cases.[14,15] Glycosuria with or without hyperglycaemia has been observed in few studies showing the metabolic changes and renal damage associated with the cholinergic effect of poisoning.[16]

Many theories have explained the hyperglycemia, as a summation of several mechanisms. Continuous cholinergic stimulation resulting in catecholamine excess along with enhanced release of ACTH from the anterior pituitary underlie this hyperglycemia. Increased glycogenolysis and neoglucogenesis also contribute to this increased cholinergic stimulation.[12,16,20,21] Sabzghabaee, et. al, in their study found significant differences in severity of poisoning in hyperglycaemic patients compared with normoglycemic patients[22]. Patients in grade III were more in the hyperglycemic groups. Acute poisoning induced hyperglycemia in this study revealed that admission blood glucose levels may be a predictor of hospital morbidity and mortality.

In the present study, more cases with raised RPG values were observed in severe grades (increasing POP score) of poisoning, highlighting the worsening effect of the poison on the glycemic status of the cases. However, such result was of short duration and reverted back to near normal values on the day of discharge. This may be due to manifestations of glucocorticoid, ACTH and catecholamine excess, resulting from stress, a cholinergically mediated effect[23] during the episode, which is also explained by the normalisation of blood sugar at discharge. Liver enzymes registered raised value above upper limit of normal in 21 cases and serum creatinine >1.5 mg/dl was observed in 12 cases showing the toxic effect on liver and kidney tissue, but their relation with hyperglycemia has not been ascertained. A study from South Korea comprising of 118 patients with OP poisoning (109 without diabetes mellitus and 9 with diabetes mellitus), there was no significant difference in the mortality between these two groups.[24] In another study done in Taiwan, increased occurrence of new onset diabetes mellitus was not observed in both acute and chronic exposure to OP poisoning.[25]

The OP compounds are involved in generating reactive oxygen species and lower the lipid content of the RBC membrane, resulting in its damage.[8] In the present study, the rise in serum MDA was significant among different grades but random plasma glucose had no association with serum cholinesterase at the time of admission or with total dose of atropine required .

The increased requirement of atropine which indirectly reflected the morbidity and severity of poisoning is in agreement with the study conducted by Makwava Prakash et al.[26] Though a number of hormones have been shown to be reduced in follow up study[23] by Dutta et al. in 2015, the effect of insulin, epinephrine and glucocortcoids may be taken into consideration in future and follow up of these cases for other OP poisoning related endocrine

issues.

A decline in serum cholinesterase activity is associated with raised mortality in OP poisoning, yet transient, self limited, reversible hyperglycemia and glycosuria, at the time of admission may identify the severity of poisoning. Though the time lag of poisoning and starting of treatment could not be traced out, yet keeping in view this metabolic effect, the suspicion of future development of diabetes mellitus, due to precipitation of occult or latent diabetics or in chronic exposure cases, cannot be ruled out. However the reversible nature of hyperglycemia also points towards multiple factors which warrants regular follow up of these patients for future early detection of diabetes mellitus.

The limitations of this study include inability to trace out duration of poisoning before initiation of treatment, hence their relation with hyperglycemia and glycosuria. The inability to identify the nature of OP compounds restricted the study to identify if any particular compound had a predisposition towards hyperglycemia. Also incipient diabetes could not be separated out from the study as we had no previous information regarding the random plasma glucose levels of each individual.

CONCLUSIONS

A decline in serum cholinesterase activity is associated with raised mortality in OP poisoning, yet transient, self limited, reversible hyperglycaemia and glycosuria, at the time admission may identify the severity of poisoning. Though the time lag of poisoning and starting of treatment could not be traced out, yet keeping in view this metabolic effect, the suspicion of future development of diabetes mellitus, due to precipitation of occult or latent diabetics or in chronic exposure cases, cannot be ruled out. However the reversible nature of hyperglycemia also points towards multiple factors which warrants regular follow up of these patients for future early detection of diabetes mellitus.

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