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A Study of Changes in Liver Function, Pancreatic Enzyme Levels, and Creatine Phosphokinase Level in Cases of Acute Organophosphorus Poisoning

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Abstract

Organophosphorus (OP) compounds are widely used insecticides in this part of the world. Organophosphorus compounds are responsible for a majority of suicidal attempt in India due to its easy availability. To determine the effect of organophosphorus compounds on hepatobiliary, pancreas, and muscular system and association of biochemical markers of respective systems to determine the outcome. This is a single-center, observational, prospective study conducted on 150 organophosphorus (OP) poisoning patients diagnosed clinically and with circumferential evidence. After admission, relevant biochemical markers of respective systems were done with standard guidelines. In patients where abnormality was found in serum amylase and lipase levels, ultrasonography and/or contrast-enhanced computed tomography evaluation of abdominal organs was done as per clinical indication. Among 150 patients, 17 (11.33%) patients succumbed to death. A significant association was observed between lipase level and treatment outcome. The odds ratio of death among high-level lipase group was 11.54 times higher than normal lipase group. Only four patients developed isolated creatine phosphokinase elevation with features suggestive of rhabdomyolysis. Isolated hepatic enzyme derangements found in only one case, whereas 5 patients had concurrent elevated lipase level. Organophosphorus-induced pancreatitis with or without hepatitis is often overlooked in acute poisoning which may be fatal. An early intervention often reverses this dreaded complication.

Keywords: Chemical Hepatitis, Creatine Phosphokinase, Lipase, Organophosphorus Poisoning

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1. Introduction

It was a German scientist, Schrader, (Aring, 1942) whose initial research led to the future development of over 2000 organophosphorus (OP) compounds, including tabun, tetraethyl pyrophosphate, Diethyl phosphate and sarin. Until now, about 50,000 organophosphorus compounds have been developed for potential use as pesticides worldwide. Organophosphorus compound poisoning is an important preventable public health problem in developing countries. Though accidental poisoning including mass poisoning can occur following ingestion, inhalation, or other routes of exposure, serious poisoning often follows suicidal ingestion (Bertolote *et al.,* 2006). World Health Organization has estimated that the incidence of organophosphorus insecticide poisoning worldwide is 3 million per year with approximately 300,000 deaths (WHO, 2004). The case fatality rate following deliberate ingestion of organophosphorus insecticides in developing countries in Asia is approximately 20% (Jeyaratnam, 1990). However, with an improvement in the standard of supportive care, particularly artificial

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ventilation, the case fatality rate is declining even in the developing countries.

Drinking organophosphorus insecticides (mainly chlorpyrifos, triazophos, or parathion) with suicidal intent has been, for the last 30 years, the most common form of poisoning in the lower socioeconomic strata in our country (Bawaskar and Joshi, 2005). A recent study has demonstrated that the incidence of organophosphorus insecticide poisoning is increasing and now accounts for over 70% of all poisonings (Eddleston, 2000).

Previously, various studies were conducted regarding mortality, morbidity, and clinical manifestations of organophosphorus toxicity. Multisystemic manifestations of organophosphorus toxicity were highlighted in these studies, including cardiovascular, neurological, and respiratory systemic manifestations (Agarwal, 1993; Anand *et al.,* 2009). Apart from few case reports, very few studies were conducted till date to evaluate the effect of organophosphorus compounds on hepatobiliary system and pancreas (Goud *et al.,* 2012; Moore and James, 1981). A cause and relationship between exposure and development of acinar cell injury have been demonstrated in experimental animal model after infusing intravenous infusion of diazinon and secretin (Mishra *et al.,* 2013). The pathology behind the development of acute pancreatitis in patients after organophosphorus ingestion is not very clear. Pancreatic ductal hypertension and stimulation of exocrine, pancreatic secretion secondary to cholinergic stimulation are considered to be responsible for the development of pancreatitis (Dressel *et al.,* 1982). Furthermore, organophosphates such as echothiophate, which inhibit the two cholinesterase isoenzymes (butyrylcholinesterase and acetylcholinesterase) in the human pancreas, increase pancreatic sensitivity to acetylcholine. Liver involvement observed in these patients was mostly secondary to pancreatic involvement.

2. Aims and Objectives

To explore if acute ingestion of organophosphorus produced acute liver damage, pancreatic damage, or muscle damage.

3. Materials and Methods

A hospital-based, observational, prospective study was conducted among organophosphorus poisoning cases admitted to the medical ward and ICCU at Burdwan Medical College and Hospital, West Bengal, from December 2012 to December 2013. In total, 150 numbers of OP cases were included after noting the inclusion and exclusion criteria. The patients present with a valid history of OP poisoning (poison material/packet) without any prior treatment were included in this study. An initial bolus dose of 3-5 ampoules is used (each ampoule containing 0.6 mg) with subsequent dose doubled every 5 min until atropinization is achieved. When the patient achieves most (at least 4 out of 5) of the target and points for atropine therapy, i.e., fully atropinized, an iv infusion at the rate of 0.02-0.08 mg/kg/h is used to maintain the therapeutic effect of atropine. The patient with a past history of chronic liver disease, pancreatitis, myopathy, malignancy, autoimmune diseases, and alcohol intake were excluded. The unknown poisoning with OP cases was not included for confounding variables. Informed consent form was filled up by patient's close relatives. They were informed about the study objectives, procedure, risk, and benefit related to this study. In addition, they also informed that the participation was optional and it did not affect the treatment outcome during hospital staying. The sample was collected aseptically by a single prick after initial resuscitation, from a peripheral vein without tying any tourniquet. During the treatment, intramuscular injections were avoided. After admission, following blood tests were done with standard guidelines, e.g., hemoglobin%, Total Counts, Differential Counts, C-reactive protein, urea, creatinine, lipid profile, serum Na, serum K, serum Ca, Creatine Phosphokinase (CPK), bilirubin (conjugated and unconjugated), albumin, globulin, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, amylase, and lipase. In patients where abnormality was found in serum amylase and lipase levels, Ultrasonography (USG) and/or contrast-enhanced Computed Tomography (CECT) evaluation of abdominal organs was done as per clinical indication. Viral serological markers such as hepatitis B surface antigen, anti-hepatitis C virus IgM, anti-hepatitis A virus IgM, and anti-hepatitis E virus IgM were done in patients with abnormalities in their liver enzymes. Liver function test along with prothrombin time/international normalized ratio was done in these patients at regular interval to monitor the progression of the disease. Ethical permission for this study was taken from the institutional ethical review committee. After collection, all data were checked thoroughly for consistency and completeness.

Statistical Package for Social Sciences (SPSS) for Windows version 11.5 (SPSS Inc, headquartered in Chicago, IL, USA) was used to analyze the data. All the data were expressed as mean ± standard deviation, frequency, and percentage as appropriate.

4. Results

Of 150 subjects, 64 (42.67%) were males and 87 (57.33%) females with a mean age of 27.6 years. Maximum cases 63 (42%) belonged to 21-30-year age groups after a group of 11 to 20 years' age 44 (29.33%). In this study, maximum cases 93 (62%) were literate and majority belongs to females and they were homemakers 46 (30.67%). Among the males, maximum were farmer 42(28%) and student 33 (22%) by their daily activity. A total of 55% were married and 40% were unmarried among cases.

According to the mode of poisoning, 143 (95%) cases taken OP for suicidal attempts, and only 7 (4.67%) cases were found accidentally poisoning. Only six poisoning cases were found skin as the route of exposure and other poisoning by per oral ingestion. The route of exposure by eye was found in only one case in this study. The most common OP compound found to be abused among this study group was chlorpyrifos in 67 (44.67%) patients, which is an agricultural pesticide. Around 51 (34%) cases were found with abuse of methyl parathion (folidol), the cough syrup (Figure 1). Other compounds identified are Sumithion (12.67%), Temphos (4%) and Fenthion (1.3%).

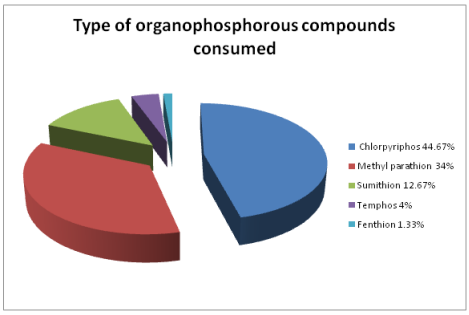


Figure 1. Types of organophosphorus compounds consumed.

The Chi-square test was performed to measure levels of significance in bivariate test and *t*-test was done to measure levels of significance in univariate test. $P < 0.001$ is test of significance in finding an association of serum lipase level with treatment outcome (Table 1). CT scan was also performed, but a CT scan did not revile any specific finding.

Among all 17 deaths, 6 persons were with high lipase level and 6 persons with normal lipase level. In total, 127 persons were cured with normal lipase level and 6 persons were cured irrespective of high lipase level. There is a significant association was observed among lipase level and treatment outcome. The odds ratio of death among high-level lipase group was 11.54 times higher than normal lipase group.

Isolated rise of CPK was noticed in four patients with features of rhabdomyolysis. CPK and other biochemical parameters are depicted as below

5. Discussion

Organophosphorus insecticides are important agents of self-poisoning in developing and developed countries alike. Rampant misuse of organophosphorus insecticides has been found in our country. It is in this background that a study was undertaken in Burdwan Medical College and Hospital, Burdwan, on 150 adult patients who have been admitted to the medical wards after consuming organophosphorus insecticides or accidental exposure to organophosphorus poison. Around 64 patients were male and 86 patients were female. The majority of the patients (63 patients) were in the age group of 21-30 years and the least (10 patients) were above 40 years. Mode of poisoning was suicidal in most patients. It was accidental in 6 patients, and no homicidal poisoning was reported. Route of poisoning was oral in maximum cases. The most common organophosphorus insecticide used was chlorpyriphos - which was implicated in 67 patients. The next common organophosphorus insecticide was methyl parathion. A total of 12 patients showed clinical evidence of pancreatitis, along with a change in pancreatic enzyme

Table 1. Association of lipase level with treatment outcome

Lipase level	Treatment outcome		Total=150	OR	95% CI		P
	Death (n=17)	Cure (n=133)			Lower	Upper	
High lipase level	6	6	12	11.54	3.18	41.87	<0.002
Normal lipase level	11	127	138				

Chi-square test was performed to measure level of significance in bivariate test. P<0.05 is test of significant in finding association of serum lipase level with treatment outcome. OR=Odds ratio, CI=Confidence interval

levels (8% of total patients). Of these 12 patients, 6 patients died. Among these 12 patients, 5 patients showed associated change in liver enzymes as well. It was noted that those who developed pancreatitis complained of pain abdomen either on the day of admission or developed pain abdomen within next 2-3 days. In these patients, alterations in pancreatic echotexture and peripancreatic collection were noted on imaging studies and the prognosis was unfavorable.

In the present study, 17 (8%) patients have shown changes in pancreatic enzyme levels. Out of these 17 patients, 9 had high lipase level. Almost all the patients had clinical pictures, suggestive of pancreatitis. A significant association was found between elevated serum lipase level and treatment outcome in cases of acute organophosphorus poisoning.

Although it is uncommon, pancreatitis has been consistently associated with acute organophosphorus poisoning. Nevertheless, because the diagnosis of pancreatitis is often established by the detection of an increased level of serum amylase, quite often the roles of salivary gland overstimulation and/or of acidosis both present in the acute organophosphorus poisoning has been overlooked as a cause of the elevation of levels of serum amylase. In addition, in most reports, there is no information on the possible alternative cause of pancreatitis, including anoxia, hypoperfusion, infection, and concurrent treatment. The latter is important for a differential diagnosis of toxic pancreatitis because about 5% of cases of acute pancreatitis are related to commonly used drugs (Greenberger *et al.,* 1998). Transient hyperglycemia and glycosuria, which are often found in severe OP poisoning, are also common in acute pancreatitis (Namba, 1971). In our present study, significant association was found between serum lipase level and treatment outcome. As the serum lipase level ismore specifically indicated pancreatic pathology and have a significant association with mortality in this study, pancreatic function assessment and treatment should be considered a routine practice in managing acute organophosphorus poisoning.

In our present study, it was noted that those who developed pancreatitis had complaints of pain abdomen either on the day of admission or developed pain abdomen within next 2-3 days. In the patients where associated alterations in pancreatic echotexture and peripancreatic collection were noted, the prognosis was not favorable.

Total 6 patients out of 12 patients with altered pancreatic enzyme profile expired. All the deaths occurred within the first 7 days of admission (Figure 2). In these 6 patients, one patient developed aspiration pneumonia with convulsion due to toxic effect of the organophosphorous compounds in the central nervous system. The rest of the 5 patients developed hyperglycemias, glycosuria, deterioration in renal function and features of noncardiogenic pulmonary edema, and succumbed to death.

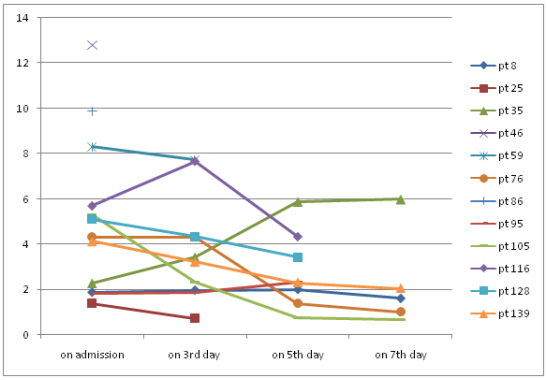


Figure 2. Graphical representation of changes in level of serum lipase in patients having features of pancreatitis (values are represented in hundreds).

In rest 6 patients, there was initially elevation in serum amylase and lipase levels; the patients also developed features of pancreatitis clinically within first 48 h. Maximal elevation in enzyme levels was noted within the 3rd day of ingestion. Ultrasonographic evaluation in most of the patients has shown heterogeneous pancreatic echotexture mostly without peripancreatic collection. Usually, the enzyme levels started decreasing within the 5th day and the patient became hemodynamically stable within the 7th day and oral feeding was also started accordingly. In these patients, associated renal function was within normal limit throughout the period.

The hypothesis has been formulated that link the pathophysiology of a triad of pancreatitis, hyperamylasemia, and hyperglycemia in acute and severe organophosphorus poisoning (Haubenstock *et al.,* 1983).

Cases with acute pancreatitis as a complication of organophosphate exposure have been reported in the literature. Ahmed *et al.*, (2009) conducted a descriptive study at the Medicine Department, Abbasi Shaheed Hospital, Karachi, during 6 months from June 16, 2006, to December 16, 2006. All patients of both sexes and ages above 15 years admitted with a positive history of Organophosphate Poisoning (OP) were included in

the study. Among 90 patients, hyperamylasemia was found in 28 (31%) patients. Hyperlipasemia was seen in 9 (10%) patients and pancreatitis was seen in 2 (2.2%) patients. It had been concluded that hyperamylasemia is more frequently seen in organophosphate poisoning while two patients proved to have acute pancreatitis as a complication (Ahmed *et al.,* 2009).

Singh *et al.*, (1997) carried out a prospective study in PGIMER, Chandigarh, India, between June 2001 and June 2005, to find the incidence of hyperamylasemia and acute pancreatitis in patients with OP poisoning. Of the 79 patients studied, serum amylase was found to be elevated (>200 S.U) in 37 patients (46.95%); among them, in three patients, it was 800 S.U. One of them showed swollen pancreas on USG, which was confirmed by computerized tomography. In the other two patients, evidence of pancreatitis was not observed. There was no significant correlation between the nature of the compounds (OP or carbamates), duration and severity of cholinergic syndrome, and increase in serum amylase. It has been concluded that mild elevation of serum amylase is common in patients with OP poisoning; however, acute pancreatitis is rare (Singh *et al.,* 1997).

Sahin *et al.*, (2002) conducted a prospective study in the Department of Internal Medicine, University of Yuzuncu Yil, Medical Faculty, Van, Turkey, in 2002, to find the prevalence of pancreatitis in OP poisoning. Four of the total 47 patients with acute OP poisoning had obviously elevated amylase and lipase levels (amylase >300 U/L; lipase >60 U/L). Only two of the patients with amylase levels between 100 and 300 U/L had elevated levels of lipase. None of the patients with normal amylase levels had elevated levels of lipase. A total of 12.76% was diagnosed as acute pancreatitis (Sahin *et al.,* 2002).

In our present study, total six patients have shown changes in liver function tests. Among the six patients, five patients have shown associated change in serum pancreatic enzyme levels and after detailed sonographic and computed tomographic and viral serological evaluation, it was concluded that either this change was secondary to pancreatic involvement although direct effect of the organophosphorus compound on liver parenchyma cannot be excluded. Only one patient has shown isolated elevation in liver enzymes and bilirubin. In this patient, no isolated obstructive or viral etiology was established and ultimately chemical substance-induced hepatitis was suspected.

In our study, serum CPK level change was observed in total 4 patients. Isolated CPK change was observed in four patients. Of these four patients, one cured and rest expired. Initially, these patients had shown deterioration in renal function though it was corrected on the progression of the disease process (Figure 3). CPK elevation in acute organophosphorus poisoning generally observed in two different clinical settings, as a part of intermediate syndrome or reflecting the results of rhabdomyolysis.

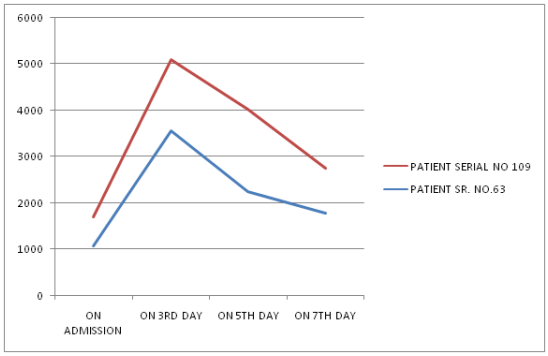


Figure 3. Graphical representation of the levels of serum creatine phosphokinase level in selected patients having isolated raised level of serum creatine phosphokinase on the initial day investigation.

Intermediate syndrome (type 2 paralysis described by Senanayake) occurs 24–96 h after poisoning with organophosphorus compounds, following the acute stage of cholinergic crisis (Senanayake and Karalliedde, 1987). The cardinal feature of the syndrome is muscle weakness affecting motor cranial nerves, neck flexors, and proximal limb muscles and is frequently associated with respiratory insufficiency. Deep tendon reflexes are usually absent. Prognosis for recovery is good and occurs within 18 days. However, death is usually due to respiratory muscle paralysis. The proper etiological basis of intermediate syndrome is yet to be established, different mechanisms such as nicotinic receptor stimulation; lack of use of oximes in initial days of treatment has been suggested as the etiological basis in different studies. In our present study, no neurodeficit was observed in any patients with elevated CPK level so that the intermediate syndrome can be excluded as etiology behind CPK elevation.

The exact clinical, pathological association between organophosphorus poisoning and rhabdomyolysis is yet not established, but vigorous fasciculation in the initial few hours of poisoning with subsequent muscle injury may have some role. Futagami *et al.*, (2001) reported a case of rhabdomyolysis as a complication of OP poisoning.

The case was complicated by acute renal shutdown and managed by hemodialysis (Futagami *et al*., 2001). In a recent study, role of CPK as an independent predictor of morbidity has been emphasized though our study does not find the same association (Bhattacharyya *et al.,* 2011).

6. Summary and Conclusion

It can be suggested that in future a more detailed study on acute organophosphorus poisoning, that will cover the infrastructural lacunae of this present study, is needed. This is more so because acute organophosphorus insecticides poisoning accounts for more than 75% of all cases of acute poisoning in hospital practice in our country. Organophosphorus-induced pancreatitis with/without hepatitis that often accompanies acute organophosphorus insecticide poisoning may be serious and sometimes fatal. However, these complications are potentially reversible and respond to treatment if they are recognized early and treated promptly and adequately.

7. References

1. Aring C. The systemic nervous affinity of triorthocresyl phosphate (jamaica ginger palsy). Brain. 1942; 65:34–47.
2. Bertolote JM, Fleischmann A, Butchart A, Besbelli N. Suicide, suicide attempts and pesticides: A major hidden public health problem. Bull World Health Organ. 2006; 84:260.
3. World Health Report 2004. Geneva: WHO; 2004.
4. Jeyaratnam J. Acute pesticide poisoning: A major global health problem. World Health Stat Q. 1990; 43:139–44.
5. Bawaskar HS, Joshi SR. Organophosphorus poisoning in agricultural India − Status in 2005. J Assoc Physicians India. 2005; 53:422–4.
6. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM. 2000; 93:715–31.
7. Agarwal SB. A clinical, biochemical, neurobehavioral, and sociopsychological study of 190 patients admitted to hospital as a result of acute organophosphorus poisoning. Environ Res. 1993; 62:63–70.
8. Jorens PG, Robert D, van Thielen G, van Brabant J. Impressive but classical electrocardiograph changes after organophosphate poisoning. Clin Toxicol (Phila) 2008; 46:758–9.
9. Anand S, Singh S, Nahar Saikia U, Bhalla A, Sharma YP, Singh D. Cardiac abnormalities in acute organophosphate poisoning. Clin Toxicol (Phila). 2009; 47:230–5.
10. Goud M, Nayal B, Deepa K, Devi OS, Devaki RN, Anitha M. A case of acute pancreatitis with occupational exposure to organophosphorus compound. Toxicol Int. 2012; 19:223–4.
11. Moore PG, James OF. Acute pancreatitis induced by acute organphosphate poisoning. Postgrad Med J. 1981; 57:660–2.
12. Mishra A, Pandya HV, Dave N, Mehta M. Multi-organ dysfunction syndrome with dual organophosphate pesticides poisoning. Toxicol Int. 2013; 20:275–7.
13. Dressel TD, Goodale RL Jr, Zweber B, Borner JW. The effect of atropine and duct decompression on the evolution of diazinon-induced acute canine pancreatitis. Ann Surg. 1982; 195:424–34.
14. Greenberger NJ, Toskes PP, Isselbacher KJ. Acute and chronic pancreatitis. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al. editors. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw Hill; 1998. p. 1741–52.
15. Namba T. Cholinesterase inhibition by organophosphorus compounds and its clinical effects. Bull World Health Organ. 1971; 44:289–307.
16. Haubenstock A, Hruby K, Jäger U. More on the triad of pancreatitis, hyperamylasemia, and hyperglycemia. JAMA. 1983; 249:1563.
17. Ahmed A, Begum I, Aquil N, Atif S, Hussain T, Vohra EA. Hyperamylasemia and acute pancreatitis following organophosphate poisoning. Pak J Med Sci. 2009; 25:957–61.
18. Singh S, Wig N, Chowdhury D, Sood NK, Sharma BK. Changing pattern of acute poisoning. J Assoc Physicians India. 1997; 45:194–7.
19. Sahin I, Onbasi K, Sahin H, Karakaya C, Ustun Y, Noyan T. The prevalence of pancreatitis in organophosphate poisonings. Hum Exp Toxicol. 2002; 21:175–7.
20. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. N Engl J Med. 1987; 316:761–3.
21. Futagami K, Hirano N, Iimori E, Motomura K, Ide M, Kataoka Y, *et al.* Severe fenitrothion poisoning complicated by rhabdomyolysis in psychiatric patient. Acta Med Okayama. 2001; 55:129–32.
22. Bhattacharyya K, Phaujdar S, Sarkar R, Mullick OS. Serum creatine phosphokinase: A probable marker of severity in organophosphorus poisoning. Toxicol Int. 2011; 18:117–23.

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