CHAPTER V

DISCUSSION
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Organophosphorus pesticides (OP) are frequently used in agriculture, forestry and public health. More than 100 individual compounds from this group are commercially available. These toxic chemicals are easily accessible thus frequently used for suicidal purposes. They enter the body via skin or inhalation during occupational exposure. Some of the OP are very hazardous due to their high acute toxicity eg. Parathion etc.

Direct exposure to pesticides is encountered by persons engaged in manufacture, formulation, transport and application of pesticides. Due to changes in socio-economic environment there is undue stress and psyche socio trauma on the individuals. These factors in many susceptible individuals are responsible for large scale abuse of pesticides as poisons for suicidal and homicidal purposes. Since 1963, there has been a steady increase in the incidence of Organophosphorus poisoning cases in India. (Seth, 1991)

The study was therefore undertaken to evaluate indepth the factors responsible for the incidence of acute organophosphorus poisoning cases and to elucidate the influencing factors i.e. the intention of poisoning, the socio economic status of victims, the precipitating factors. Patients were observed in hospital and a group of them was followed upto 25-50 weeks to correlate the clinical and biochemical alterations and finally the outcome of the treatment of patients.

A total of 121 organophosphorus poisoning cases 14 – 72 years with male to female ratio of 2:1 were included in the study. In the present study the most frequent occurrence of poisoning was in the third decade (48.8%) followed by the second decade (30.6%). The peak incidence of suicide as reported by Quinby (1964), Balani et al. (1968) and Gupta and Patel (1968) was also in the third decade, whereas the incidence described by Viswanathan and Srinivasan (1962)
were similar in both the second and third decades. Sunder Ram (1991) reported 94% cases in the age group of 15 – 40 years. This could be probably due to the fact that the age group of 21 – 30 years is the most critical period specially in moment when one is likely to face various problems e.g. marriage adjustment and employment etc. that may lead to psychological stress and ultimately force a person to take ultimate step to end his life by consuming available poisons.

In the present study males were more likely to expose to OP poisoning ( M:F :: 2:1). Similar observations were reported by Mutalik et al. (1962), Gupta and Patel (1968), Mehta et al.(1971), Balani et al.(1968) and Agarwal (1993), while Viswanathan and Srinivasan (1962) and De and Chatterjee (1967) reported higher number of cases among females than males.

Educational status of poisoning cases as recorded in the present study is more or less similar as reported earlier by others, De and Chatterjee (1967) and Agarwal (1993).

The commonest intention of poisoning (suicidal) in the present study is very much similar with the studies reported by Chhabra et al (1970); Mehta et al.(1971) and Karalliedde et al (1988). Agarwal (1993) has occupational exposure in 16.8% of the cases and accidental ingestion in 15.8%. In this study OP compounds were consumed by 80.2% cases with the intention of committing suicide. Occupational exposure was the source in 9.1% of the cases, and only 6.6% of cases were associated with accidental consumption. However Quinby (1964) reported that 50% of the cases resulted from occupational exposure, followed by 45.4% from accidental exposure and only 4.6% cases by intentional suicide.

In the present study the commonest precipitating factors among suicidal cases include domestic problems (29.9%), marital friction (13.4%), financial stress
(11.3%), love affairs (11.3%) and job problems (8.2%) are more or less similar as reported by Desai (1983) and Agarwal (1993).

The observed symptoms and signs, to a great extent are secondary to cholinesterase inhibition. The usual symptoms include headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps, diarrhea, and discomfort in the chest. Signs also include sweating, miosis, tearing, salivation and other excessive respiratory tract secretions, vomiting, cyanosis, papilledema, uncontrollable muscle twitches followed by muscular weakness, convulsions, coma, loss of reflexes, and loss of sphincter control. The last four signs are seen only in severe cases but do not preclude a favourable outcome if treatment is prompt and energetic. (Hayes and Laws, 1991)

BEHAVIOURAL EFFECTS
In the clinical cases of poisoning by OP, the behavioral impairments have been characterized by the following symptoms: Fatigue, irritability, coordination difficulties and slow thinking process, Brower et al (1964). Metcalf and Holmes (1969), Durham et al (1965) investigated in humans the behavioral effects of exposure to OP compounds. Namba (1971) reported motor defects including tremors, muscular twitching and muscular fasciculations in acute OP poisoning cases.

In the present study all the survived cases were evaluated for psychiatric assessment clinically after they recovered from acute OP poisoning and atropine was discontinued. Decrements in alertness and memory, increased irritability, memory deficit, lethargy and lack of energy were observed in only 6 cases (4.9%). It is possible that neurobehavioural manifestations of organophosphorus toxicity observed in the present study may be attributable to accumulation of acetylcholine.
at central and peripheral synapses as a result of cholinesterase inhibition. The onset of behavioral disturbances was also temporarily coincident with the decline in ChE levels, Levin and Rodnitzky (1976). These observations however need to be substantiated by means of objective parameters such as EEG and electrophysiological changes so that they can be used for early detection of health impairment from exposure to OP compounds.

CARDIAC TOXICITY

Various ECG abnormalities such as Sinus bradycardia, sinus tachycardia, depression of ST segment and inversion of T-wave were observed in present study in 46 out of 121 cases (38.01%). Similar were the reports by Singh et al, 1969; Namba et al, 1970; Chhabra et al, 1970; Khandekar, 1971. Cardiac toxicity consists of two phases, the first appearing as a brief phase of intense sympathetic tone, manifested by sinus tachycardia. This phase is followed by the second phase of parasympathetic discharge often manifested by varying degrees of A.V. block. There have also been reports of non specific ST-T wave abnormalities as well as terminal ventricular fibrillation. Organophosphorus compounds may produce a third type of cardiac toxicity such as a prolonged QT interval with torsade de pointes arrhythmia and pleomorphic ventricular tachycardia. The "long QT interval – Torsade syndrome" is believed to be caused by an intense unequal sympathetic stimulation of myocardial fibres, Abraham and Dhar (1995).

In the present study sinus bradycardia (6.6%) sinus tachycardia (24%) and depression of ST segment with inversion of T-wave in 7.4% of cases were observed. Earlier Agarwal (1993) had similar observations in his study of 190 acute organophosphorus poisoning cases.
Faerman (1985) traced the conditions of 179 persons employed in an OP compound production plant and reported bradycardia and sinus arrhythmia. According to the author the E.C.G. and Oscillographic studies suggested the presence of an increased vagus tone. Saiyed et al. (1984) studied cardiac changes in 155 male pesticide formulators, exposed to organophosphate insecticides and found that 24 (15.4%) of the exposed and 4 (6.7%) of the control subjects had abnormal heart rates (Bradycardia and tachycardia) while 20 (12.9%) of the exposed subjects had abnormalities of rhythm conduction a tall R wave and of ventricular bigeminy or trigeminy. Ludomirsky et al. (1982) has observed Q-T prolongation in 14 and malignant tachyarrhythmias in 6 and suggested that careful ECG monitoring is necessary until the Q-T interval returns to normal. According to the Kaloyanova and Batawi (1991) the ECG has shown bradycardia and sinus arrhythmia and suggested the presence of an increased vagus tone. Chhabra et al. (1970) and Ottevanger (1976) reported that the bradycardia may be due to the effect of ChE inhibitors acting either directly on the myocardium and the conducting tissues or through a neurogenic mechanism.

**ChE–ACTIVITY**

In OP poisoning, ChE inhibition results from the binding of phosphate radicals of OP to the enzyme active site forming phosphorylated enzyme. The pharmacologic and toxicologic effects of OP are probably largely due to inhibition of AChE resulting in excess accumulation of ACh at the cholinergic synapse. This overabundance initially stimulates and subsequently paralyses cholinergic synaptic transmission in the CNS, somatic nerves, autonomic ganglia, parasympathetic nerve ending and some sympathetic nerve endings. Onset of symptoms are most
rapid following inhalation and ingestion of the compound. Fortunately the enzyme cholinesterase is also present in the circulating blood both in RBC and Plasma, although no satisfactory account of the role of this high concentration enzyme in the blood is given. Its presence is used as a parameter in assessing the exposure to organophosphorus compounds and also in prevention, diagnosis and treatment of poisoning cases from these chemicals.

Estimation of erythrocyte AChE is theoretically preferred as the most accurate reflection of the degree of synaptic ChE inhibition in nervous tissues, Coye et al. (1986). The measurement of blood ChE activity gives useful information on the clinical state of persons poisoned by Organophosphorus compounds. Kashyap and Gupta (1976)

ChE activity correlates well with the amount of pesticides absorbed in the organism and its inhibition level is also related with toxic manifestations in the body. It was apparent that the depression of the ChE activity was marked in those exposed subjects showing specific gastrointestinal and cardiorespiratory symptoms; Namba (1971); Namba et al. (1971); Kashyap and Gupta (1976). It has also been reported that when plasma ChE activity depression analyzed age and sex wise did not show any significant difference indicating the susceptibility of all the individuals is similar irrespective of their age and sex.

In the present study, erythrocyte AChE activity and plasma ChE activity was evaluated immediately after the admission of acute OP poisoning cases. The values were compared with age match controls. It was observed that there was a significant inhibition in plasma ChE activity in survived OP poisoning cases, this was more evident in cases which expired even after treatment. Similarly, a significant inhibition in erythrocyte AChE activity was seen in OP poisoning cases when compared with age matched controls. The fatal cases showed more decline
in AChE activity as compared to survived cases. This data also suggests that with
the plasma ChE activity and erythrocyte AChE are being affected significantly
when compared with control.

The data in the present study also confirmed the earlier findings of Kashyap and
Gupta (1976) that the decline is almost similar in all the cases. Age and sex does
not have any effect on the declining pattern of these two enzymes. In this study this
was also observed that a correlation exists between the levels of decline in AChE
and ChE activity and the symptoms recorded in these patients. The more the
decline in the levels of these enzymes the more severe symptoms were seen in
patients.

HAEMOGRAM
In the present study a complete haemogram which included (Hb%, TLC,DLC and
ESR) was done in all 121 cases. The results suggested that there is no alteration
in Haematological parameters. Similar observations were recorded by Kashyap
and Gupta (1976).

However, among the OP insecticides, parathion has been reported to produce
aplastic anaemia - Christophe (1969) and also during chronic exposure
especially when combined exposure takes place leucopenia has been reported by
c polymorphonuclear leukocytosis in advanced state of OP exposure while
leukocytosis has been mentioned as one of the laboratory finding by Hayes (1982).

RENAL FUNCTION TEST
In the present study, routine urine examination, microscopic examination was done
in all 121 cases. However, no abnormality was seen in the present study, similar
were the observations by Mutalik et al (1962), and Gallo and Lawryk (1991).
Further blood urea, serum creatinine and electrolytes (Na & K) were also done in all 121 cases but no alteration was observed in any of these tests.

Although Agarwal (1993) had reported a reversible albuminuria in 12.6% cases and azotemia in 18.9% cases.

LIVER FUNCTION TESTS

Liver function tests which included S. Bilirubin, S.G.P.T, S.G.O.T. and Alkaline Phosphatase were performed in all 121 cases, however appreciable alterations in their values were observed only in four cases. Only serum bilirubin showed a significant alteration when the results were compared between the values at the time of admission and discharge. In earlier studies, Namba (1971) did not find any changes in the liver function tests in patients during one month to two years of observation after their exposure.

Changes in some biochemical parameters such as alkaline phosphatase, SGOT, SGPT has been observed by Bogusz (1968), Grech (1965), Burseva (1966), Karimov (1968) in OP pesticides exposed workers in the field. However they did not mention in detail the trend in these enzymes in these workers. Lutterotti (1961) observed temporary liver damage with special mention of increased serum bilirubin levels in persons exposed to OP insecticides. It is therefore presumed that OP insecticide do affect the liver functions but the effects are transitory and chances of recovery are more if the patient after proper treatment recovers from the acute effect of OP poisoning.
LACTATE DEHYDROGENASE

Lactate dehydrogenase is directly linked with glucose metabolism. It is a very widely distributed enzyme being found in all organs of our body, but is especially plentiful in cardiac and skeletal muscle, liver, kidney, and red blood cells. Although there is no direct report of alteration of lactate dehydrogenase in cases of organophosphorus poisoning. In the present study it was observed that the average LDH values among the cases who died due to Organophosphorus poisoning were significantly higher (P<0.05) as compared to the case who survived after this poisoning, suggesting that in organophosphorus poisoning the alteration in LDH enzyme may assist in projecting the prognosis of the case.

CREATINE PHOSPHOKINASE

CK activities – CK is a key enzyme of muscular metabolism. It is mainly present in skeletal muscle, myocardium, brain, gastrointestinal tract, uterus and urinary bladder.

In the present study, 24 cases of OP poisoning who survived and 12 who died due to OP poisoning, their CK activity was estimated. A significant increase in the level of CK activity and more significant alterations in the patients who died due to poisoning were seen, conforming the earlier work of Bhatt (1990). Yang (1987) and Sasaki (1998) found an increased activity of CK and CK MB among employees of OPC manufacturing factory and farmers using OPC insecticides. However, in a previous study by Sasaki in 1976, he has also found increased CK and CK MB activities in female farmers who died following Organophosphorus insecticide poisoning.

Thus it is presumed that estimation of CK activities in suspected OP poisoning cases may serve as a corroborative diagnostic criteria, along with alterations in
LDH activity when associated with the changes seen in the cholinesterase activity, the most important biochemical change seen in OP poisoning cases.

IMMUNOGLOBULINS

In the present study in 21 cases accompanied with 19 control cases were examined for any alterations in Immunoglobulins IgG, IgA and IgM and also in C3 and C4 complements. A significant alteration in IgG, IgA and in C3 and C4 complements were seen in exposed subjects when compared with the controls. OP compound causes a specific stimulation to immune system, especially IgA globulin which are selectively secreted into saliva, respiratory and intestinal mucous secretions. The site of synthesis of IgA is in submucosal plasma cells of the lamina propria of the gastrointestinal tract. Probably IgA, because of the attached secretary piece appear to be relatively resistant to digestion by proteolytic enzymes thus allowing this immunoglobulin to remain active and able to perform a protective role in the intestinal and respiratory tract.

Malathion exposed cases showed the highest level of IgG suggesting that exposure to pesticide causes alteration in Immunological profile.

In India, Karnik et al (1993) reported increased levels of IgG and IgA and corresponding increased levels of C I C (Circulating Immune Complexes) were observed in exposed groups.

The estimation of IgA levels and its increase in OP poisoning cases can serve a useful diagnostic tool. The complement system comprising plasma proteins, many of which are proenzymes and under certain conditions, are activated to enzymes. A significant increase in C3 and C4 fractions of complement are suggestive of inflammatory process going on in the body, which is the case in OP insecticide poisoning cases.
MANAGEMENT (THERAPEUTIC REGIMEN)

Inspite of increasing frequency of suicidal attempts with OP compounds, in India, no studies have been undertaken with a view to rationalize therapy. Balani et al (1968) described atropinization for a period of only 24-48 hours. The standard method utilized for OP compound poisoning by Taylor (1985), Friedman (1987) was immediate stomach wash followed by atropine in a dose of 2-4 mg l/m or l/v given every 3-10 minutes to achieve atropinization. The dose was repeated to maintain atropinization and the drug was withdrawn judiciously. Milby(1971) suggested that in moderate severe cases pralidoxime chloride along with atropine can also be used. Pralidoxime should be used l/v as an initial dose of 1 gm at a rate of not in excess of 500 mg/min. After an hour a second dose of 1 gm was indicated if muscle weakness has not been relieved. He found that together the two antidotes, atropine and pralidoxime chloride were more effective than either one alone. Patial (1993) suggested that if the patient has cyanosis it should be corrected before giving atropine.

Atropine given as 2-4 mg l/v stat dose, followed by 0.6 to 1.2 mg l/v every 5 to 30 minutes depending upon the response. A total of 75 to 150 mg of atropine to be injected in the first 24 hours. To regulate the dose atropinization of patient is essential. This is the regimen recommended in earlier textbooks on poisoning.

Cherian et al (1997) reported that use of Pralidoxime (P2 AM) alone in the management of patients with OP poisoning had no good result and thus they raised a question about the validity of the use of P2 AM alone in such cases.

Johnson et al (1996) postulated that high dose P2 AM is no more beneficial in the management of patients with OP poisoning than a 1 gm bolus dose.

In the present study 121 acute OP poisoning cases were treated. Atropine and P2AM were administered in 98 cases and 18 cases were treated with atropine
only. In 5 cases amongst the survival group, no treatment was given and were only clinically observed. The results suggest that out of 98 cases with both atropine and P2 AM, 85 cases (86.7%) survived and only 13 cases (13.3%) died. While 18 cases who were treated with atropine only 15 cases survived (83.3%) and 3 cases died (16.7%) suggested that in the combined effect of atropine and P2 AM, probability of survival increases as compared to those cases which were treated with atropine only. The results obtained with the treatment are similar as reported by Milby (1971).

It is therefore suggested that after stomach lavage the more effective treatment against OP insecticide poisoning cases will be the combined dosing of atropine and P2 AM provided patient is hospitalized early otherwise P2 AM administration does not help much. The dose schedule given to patients depends on the gravity of the case.

Eighteen cases were followed up between 25-50 weeks after discharge. The symptoms and signs of peripheral neuropathy, burning sensation of palms and feet numbness, decreased sensitivity, poor sensory localization, muscle weakness and sluggish tendon reflexes were observed. Symptomatic treatment cured the cases. No cases were diagnosed with delayed neuropathy.