Chapter

Use of Plasma Pseudocholinesterase as a Predictor of Mortality in Organophosphate Poisoning

Siva Kumar V., Shruthi K. Siva Kumar, Ipsita Debata, Tejas J. and Viswanathan K. Gowda

Abstract

The study was conducted on patients of organophosphate poisoning admitted to Bapuji Hospital (J. J. M. Medical College), Davangere during a period of October 2011 to March 2013. To know the incidence of acute Organophosphate poisoning, epidemiological aspects of the patient and plasma pseudocholinesterase levels at the time of admission and correlation within hospital mortality. Total number of cases studied were 150. At the time of admission blood was drawn for estimation of plasma pseudocholinesterase estimation. The patients were clinically divided into three grades according to Dreishbachs criteria. Analysis was performed by cobas integra 400 cholinesterase assay system. All patients were followed-up for 3 days to know the outcome. Majority of the cases (40%) belong to 21 to 30 years age group and predominantly belonged to male sex (73%). Seventy eight cases (52%) had severe poisoning, 40 cases (26.67%) had moderate poisoning and 32 cases (21.33%) had mild poisoning. Sixty cases (40%) had fatal outcome. Suicidal consumption was seen in 128 cases (85.33%). Plasma pseudocholinesterase levels associated with fatalities in severe poisoning and was found to range from 912 to 2490 U/L which accounts to suppression of plasma pseudocholinesterase levels by 84.04 to 93.19%.

Keywords: organophosphate poisoning, plasma pseudocholinesterase, butyrlycholinesterase, suicidal poisoning, agricultural poisons

1. Introduction

Poison is a substance (solid, liquid or gaseous), which if introduced in the living body or brought into contact with any part thereof, will produce ill-health or death by its constitutional or local effects or both. However, Goethe says that, 'There is no such thing as poison, it all depends on dose'.

It might be challenging to draw a line between a medicine and a poison because a medicine can behave as a poison in big amounts and can be a medicine in tiny doses. The "intent" with which they are intentionally supplied, as opposed to accidently, is the sole significant distinction.

Many people believe that toxicology, or the study of poisons, is a very young field of science. On the other hand, evidence of the damaging effects of chemicals on living things dates back to prehistory. Even in the past, mankind looked for poison antidotes. While many chemical compounds used to make medications can behave as poisons in their larger abundance, there has been an almost centuries-long risk to both human health and the environment.

In all civilised nations, poisoning incidents are steadily rising. Depending on a number of variables, the type of poison employed for distinct modalities may change. However, there has been a steady increase in accidental and suicidal poisoning in agriculture and domestic settings. The increased usage of many chemical products in the home is blamed for the increase in accidental poisoning among youngsters. Children are most likely to become poisoned in the kitchen (34%), bedroom (27%), bathroom, and laundry rooms (15%). Among children the common poisons include kerosene, household chemicals, drugs, pesticides and garden plants. Industrial poisoning is gradually receding, owing to advances in industrial hygiene and medical service and to the increasing automation of industrial processes.

In adults the manner of poisoning, irrespective of the sex can be;

1. Suicidal

2. Accidental

3. Homicidal

4. Self-treatment

5. Injudicious medication.

Poisoning can happen as a result of:

1. The use of poison for illegal objectives.

2. Ingesting poison by accident while thinking it is a harmless material.

3. Accidental or unintentional inhalation of poisonous gas.

4. Improperly mixing poison-containing medications.

5. Accidentally taking a huge dosage of medicine that is poisonous.

6. Abundant self-medication.

7. Drug addiction.

8. Being bit by a dangerous animal.

9. Food contaminated with poisons or microbes.

Criteria for an ideal suicidal Poison:
An ideal suicidal poison should be:

a. Easily available.

b. Cheap.

c. Tasteless, if not, have a pleasant taste.

d. Highly toxic and sure in action.

e. Capable of being easily consumed with food or drink.

f. Capable of producing painless death, preferably through sleep.

Opium and barbiturates satisfy several of the above criteria. But organ phosphorus compounds and endrin commonly used for the purpose. The substances like oleander seeds, oxalic acid, carbolic acid, aspirin, arsenic trioxide, mercuric chloride, or coal-gas inhalation may be used for the purpose.

Criteria for an ideal homicidal Poison:

An ideal homicidal poison should be:

a. Colourless, tasteless and odourless.

b. Capable of being easily administered in food, drink, or medicine without arousing any suspicion.

c. Should be highly toxic and certain in its effects.

d. Signs and symptoms of it should resemble a natural disease without raising any suspicion.

e. Signs and symptoms are to appear late, giving sufficient time to the culprit to escape or to avoid suspicion.

f. Having no good antidote against the poison.

g. Having no specific postmortem findings to arouse suspicion.

h. To be rendered undetectable from the body by toxicological examination.

Organic compounds of "fluorine" used as rodenticides and "thallium" satisfy several of the above criteria. However, compounds of arsenic, aconite, antimony, mercury, copper, powdered glass, oleander, nuxvomica, madar etc. may be used for the purpose of homicide.

Apart from poison those are ingested, poisoning due to animal bites especially snake bites are quite common in India. Except in Arctic lands, New Zealand and Ireland snakes are found all over the world. In India, snake bites are usually accidental in nature. Especially in southern districts of West Bengal, Orissa, Assam, Bihar, Madhya Pradesh, Karnataka, Andhra Pradesh etc., the incidence is high. At least more than 20,000 persons die per year out of 2 lakh snake bite cases in India.

Human poisoning due to suicide, homicidal, accidental is common in India, as poisons are easily obtained in the market such as insecticides, pesticides, rodenticides,

weed killers, and drugs. In addition to the above, many poisonous plants grow widely all over the country are also used in poisoning e.g., Oleander, Aconite, Nux- vomica, Calotropis, Datura, Nerium odorum, Abrus precatorius etc. Many Indians consider taking off life by poisoning a lesser crime than bloodshed Reddy et al. [1]. Incidence of accidental poisoning is also increasing because of increasing use of chemicals both for industrial and also domestic purposes. Insecticides and weed killers are also in extensive use for agricultural purposes.

Following the knowledge of the highly lethal nature of these substances they have become popular as suicidal and homicidal poisons. In Belgaum, the age-old tradition of suicides by drowning in wells or by hanging have been replaced by poisoning oneself by the use of organophosphorus compounds, etc.

1.1 Objectives

- Incidence of acute Organophosphate poisoning.
- Epidemiological aspects of the patient.
- Pseudocholinesterase levels at the time of admission and correlation within hospital mortality.

Organophosphates are a group of compounds with various toxicities to different form of life. The widest use of these compounds is as insecticides.

Organophosphate insecticides have controlled vectors of Malaria. Their use is increasing since, low toxic organophosphates are now replacing Chlorinated hydrocarbon insecticides such as DDT, which accumulates unchanged in human and animal tissues and have adverse effects.

The organophosphate insecticides are esters and oxides of phosphoric and pyrophosphoric acid which, when introduced into animal body, inhibit the enzymes that hydrolyse acetylcholine. They are called anticholinesterase agents. These inhibitors have frequently been called “irreversible” inhibitors because it was believed that the enzyme attacked by them is permanently destroyed and that recovery took place by formation of new enzyme molecules.

In India, the first report of oral poisoning by Organophosphorus compounds was reported by Mutalik et al. [2]. They studied 25 cases of Diazinon poisoning and described the various clinical features, management and autopsy findings.

Acetyl choline (Ach) an ester of choline is present in various organs and tissues of the body. It plays an important role in transmission of nerve impulses at - Synapses & Myoneuronal junction. Acetylcholine is rapidly destroyed by an enzyme Acetyl choline esterase (AchE). This enzyme stops the action of acetylcholine which is present in various body tissues; including muscles, nerve cells and red blood cells. A deficiency of cholinesterase results in neuromuscular excitability, a prominent clinical feature in.

1.2 Organophosphate poisoning

According to Dr. K.S.N. Reddy [1], the most commonly used poison in rural and urban places in South India is organophosphorus compounds, which are powerful inhibitors of cholinesterase enzyme. Inactivating it by phosphorylation at myoneuronal junction, it results in a syndrome of over activity due to excess of unhydrolysed acetyl choline at myoneuronal junction, which leads to accumulation of Acetylcholine

Concentration of AchE	Severity of toxicity
20–25%	Mild
10–20%	Moderate
<10%	Severe

Table 1.
Callaway classification based on acetylcholine esterase suppression.

at parasympathetic, sympathetic and somatic sites. Thus preventing the transfer of nerve impulses across the myoneuronal junction.

According to Callaway et al. [3], the red cell choline esterase level in good health ranges between 75 and 142 units. Mild symptoms occur when acetylcholine esterase activity reduces to 20–25% of normal. If moderate poisoning occurs, the activity of AchE decreases to 10–20% of normal. Severe poisoning results in an activity of less than 10% of normal (**Table 1**).

This clearly indicates that the rate limiting factor in a case of organophosphorus compound poisoning is the concentration of acetyl choline esterase enzyme at myoneuronal junction.

Thus the concentration of AchE at myoneuronal junction acts as a guide to determine - (i) The severity of toxicity, (ii) The therapeutic dose of atropine and (iii) PAM (Pyridine Aldoxime ethiodide), so that these antidotes, may not be used in excess quantity than required, because they themselves are capable of causing harmful effects on the body.

According to the text book of Modern Toxicology by V.V. Pillay [4], Plasma cholinesterase levels (Pseudocholinesterase) are diagnostic.

In the present study the concentration of AchE was estimated in the plasma in order to assess the severity and mortality.

Clinical Manifestations of Organophosphorus Poisoning:

Organophosphorus compound produces clinical manifestations by depression of the enzymes cholinesterase, resulting in the accumulation of acetylcholine at various receptors. This has three types of effect.

1. Cholinomimetic actions of muscarinic type at autonomic effector organs.

2. Nicotinic actions: Stimulations of all autonomic ganglion and skeletal muscle.

3. CNS effect; Stimulation with consequent depression of cholinoceptive sites in the CNS [5–7].

1.3 Classification of organophosphate poisoning based on clinical features

The severity of poisoning is graded according to modified version of Dreisbachs classification (**Table 2**) [8].

Plasma cholinesterase activity recovers slowly due to the irreversible nature of organophosphate inhibition. Without the use of pralidoxime, plasma cholinesterase rises an average of 15.6% over 14 days in one group of organophosphate-exposed workers. The serial levels rather than one initial level may be valuable in diagnosing organophosphorus poisoning. The poor correlation between acetylcholinesterase level and clinical effects may mislead clinicians, into making incorrect diagnosis of mild

Grade (Dreisbachs)	*Symptom*
Mild	1. Nausea
	2. Vomiting
	3. Diarrhoea
	4. Sweating
Moderate	1. Lacrimation
	2. Salivation
	3. Miosis
	4. Fasciculation
Severe	1. Coma
	2. Seizures
	3. Incontinence
	4. ARDS
	5. Areflexia

Table 2.
Dreisbachs criteria.

poisoning. Sequential post-exposure determinations may be necessary to confirm Acetylcholinesterase inhibition. Initially acetylcholinesterase should regenerate by 15 to 20% within 3 to 5 days [9, 10].

1.4 Anti-cholinesterase agents

These compounds are capable of inhibiting cholinesterase enzyme both true and pseudo and thus resulting in accumulation of acetylcholine at various cholinergic sites. Thus, pharmacological effects resulting from administration of anticholinesterase resemble the actions of endogenous acetylcholine or exogenously administered acetylcholine.

Classification:

1. Reversible anti-cholinesterase - physostigmine, neostigmine.
2. Irreversible anti-cholinesterase - organophosphorus compounds.

1.5 The reversible anti-cholinesterase

Reversible anticholinesterase by their structural resemblance to acetylcholine are capable of combining with anionic and esteratic sites of cholinesterase as well as with acetylcholine receptors. However, the complex which they form with the esteratic site of cholinesterase is much less readily hydrolysed from acetyl esteratic site than the complex formed with acetylcholine. This produces a temporary inhibition of enzyme.

Reversible anticholinesterase have gained therapeutic importance. They are found to be beneficial in the treatment of glaucoma, myasthenia gravis, paralytic ileus, urinary retention, in the treatment of certain cardiac arrhythmias (paraoxysmal supra ventricular tachycardia) and in Belladona poisoning.

1.6 The irreversible anti-cholinesterase

The irreversible anticholinesterase combines only with the esteratic site ofcholinesterase which is phosphorylated. The hydrolysis of phosphorylated site is extremely slow and in certain cases does not occur at all this results in irreversible inhibition of enzyme. The irreversible anticholinesterase are of limited therapeutic use because of prolonged action and high toxicity. They are found to be of great benefit in the field of agriculture, where they are used as insecticides.

1.7 Paraoxonase

Paraoxonases are a group of enzymes involved in the hydrolysis of organophosphates parathion, diazinon and chlorpyrifos [11, 12]. The important discoveries that certain organophosphorus (OP) insecticides could be enzymatically hydrolyzed by plasma and that this reaction is catalysed by enzymes which were named "A-esterases", were reported in the 1940s and 1950s. There are 3 proteins in this family which include PON-1, PON-2 and PON-3 the genes of which are located in long arm of chromosome 7 [13].

1.8 Chemical structure with classification

Organophosphorus insecticides are usually esters, amides or thiol derivatives of phosphoric or phosphonic acid. The general formula being described in **Figure 1**.

Typically, Rl and R2 are straightforward alkyl or aryl groups. The "laving group," often known as Group "X," can be any of a wide range of substituted or branched aliphatic, aromatic, or heterocyclic groups that are connected to phosphorus by a bond with some degree of liability. Typically -O- or -S-. The similar chemical is known as a phosphate or phosphorothioate, and the double bond may be O or S. Many pesticides are produced in the intrinsically more stable P=S form, which can later be transformed in vivo to the physiologically active oxon [14].

Phosphorothioate oxidation to phosphates poses a risk since phosphates are more volatile and may undergo directly harmful oxidation at higher temperatures. Some formulations (such as malathion) may become more harmful when they are isomerized while being stored in warm, humid circumstances [15].

2. Methodology

The study was conducted on patients of organophosphate poisoning admitted to tertiary care hospital at Davangere, Karnataka, India during the period between October 2011 & March 2013.

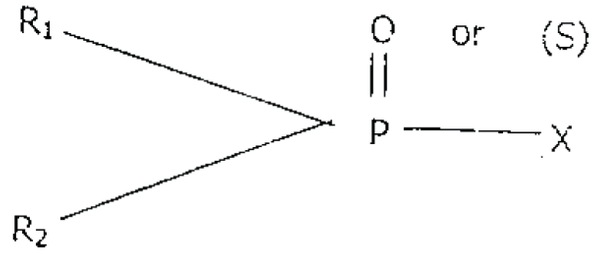

Figure 1.
Chemical structure of Organophosphate.

Materials used for the study were 18-gauge needle, 10 cc syringe, Colour coded vacutainer tubes, Cobas Integra 400 cholinesterase assay system.

Total number of cases studied were 150. At the time of admission blood was drawn for estimation of plasma pseudocholinesterase estimation. A laboratory reference range of 8000 to 18,000 U/L was used in this study which coincide with the estimated population mean levels.

Information was gathered from patient case histories, hospital MLC files, eyewitness interviews, family and friends of the dead, and the investigating officer.

The study covered patients of either sex who had Organophosphate poisoning and were older than 14 years.

All patients with age less than 14 years, poisoning other than organophosphate were excluded from the study.

From the patient, his or her relatives, and the police, a thorough history was gathered on the quantity of poison, the type of poison, etc. Whenever possible, the poison container was also examined. Each patient underwent a clinical examination, and using Dreishbach's criteria, the patients were graded into mild, moderate, and severe groups based on their signs and symptoms. All patients were followed-up for 3 days to know the outcome. In fatal cases the Forensic Science Laboratory was also used for conformation of organophosphorus poisoning. Data was wrangled using Microsoft excel 2016 and analysed with IBM SPSS v26.

3. Results and discussion

Out of 150 cases, highest number of poisonings was reported in the age group of 21 to 30 years (60 patients, 40%) as depicted in **Figure 2**. This correlates with the age which was also reported by S Singh et al., were the mean age of the patient was found to be 26.44 years [16].

Males were found to be more affected (73%) than the females (27%). Similar observations were made by Singh et al. [16], consisting of 67.95% males as depicted in **Figure 3**.

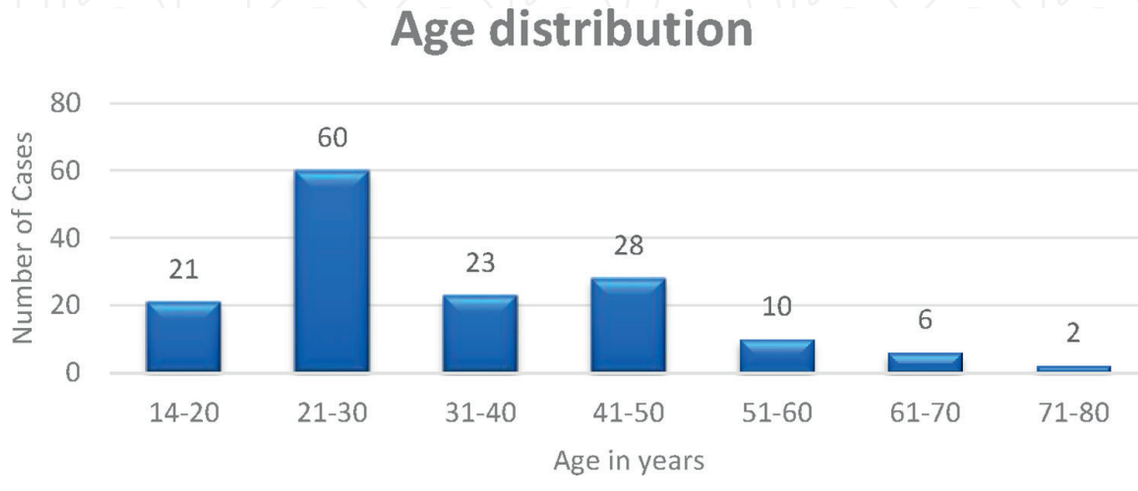

Figure 2.
Age distribution.

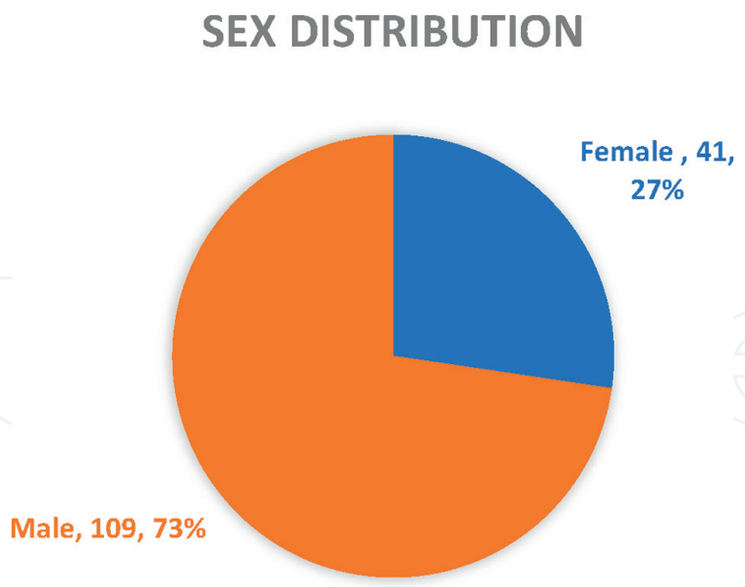

Figure 3.
Sex distribution.

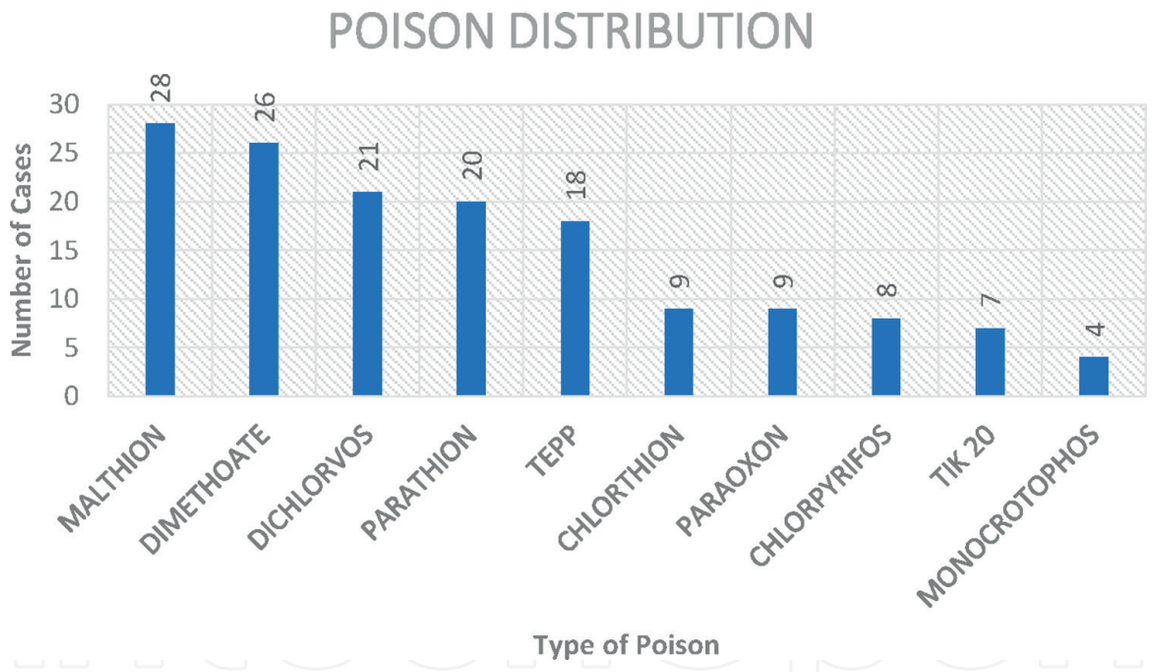

Figure 4.
Type of poison distribution.

3.1 Time taken to reach hospital

The average time taken by the patients to reach the hospital in this study was found to be 5 hours with a minimum of 1 hour and a maximum of 12 hours. This can be attributed to the inefficient health care delivery and transport systems and wide area of coverage leading to lack of access to health care services to most of the areas situated in the outskirt of the city.

The commonest poison consumed in the study was Malathion, 28 patients (18.67%) as shown in **Figure 4**. Second common was Dimethoate, 26 patients (17.33%). In every

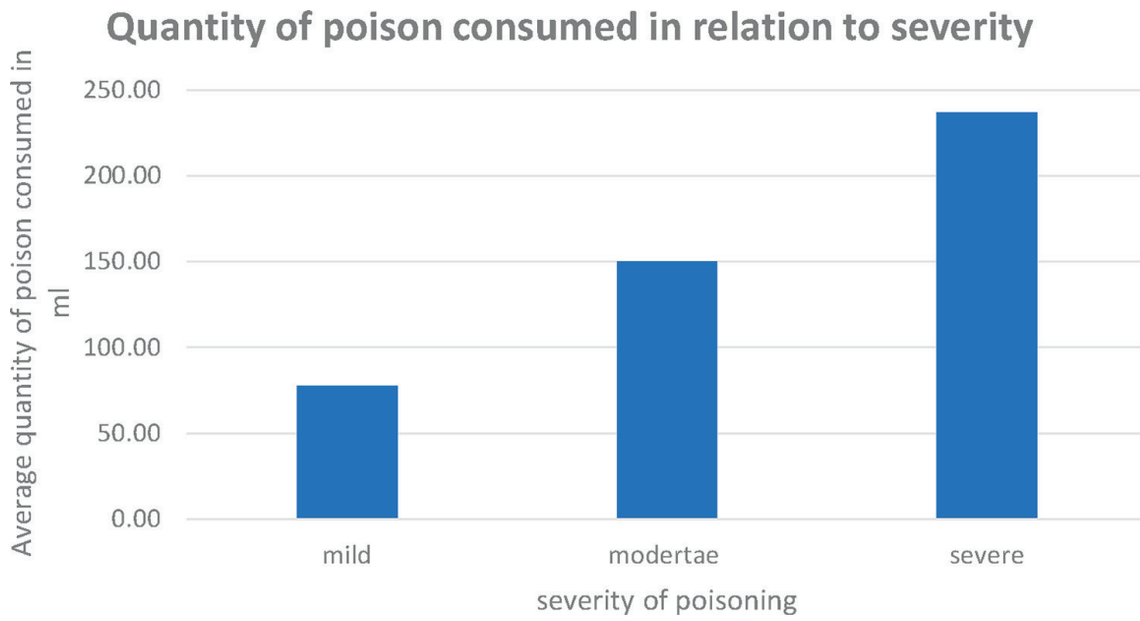

Figure 5.
Approximate quantity of insecticide ingested.

instance, the poisons were taken orally. One of the most widely used organophosphate insecticides is malathion, which is frequently accessible for agricultural application. Due to its simple accessibility to farmers and fatal action, despite its unpleasant taste, it is most frequently used orally. Other research by Namba, Greenfield and Grob [6]; Daglia & Shaikh [17]; Wadia, Bhirud, Gulavani & Amin [18] and Wille, Thiermann & Worek [19] also reflect similar finding. An acute case of demeton poisoning in a child was reported by Felsenstein and collegues [20].

Most of the participants in our study had ingested 101 to 200 ml of an organophosphorus chemical (43.33%) as seen in **Figure 5**. This amount exceeds the lethal dose for Malathion and Dimethoate, the two most prevalent poisons employed in our investigation.

In relation to severity of poisoning, the average quantity of poison consumed in case of severe poisoning was found to be 237.05 ml which could also be a causative factor in highest mortality being associated with this group as this dose in in excess of the fatal dose of most of the poisons observed in this study.

The patients were clinically examined and divided into groups using the Dreisbach's criteria 78 patients (52%) had sever poisoning, 40 patients (26.67%) had moderate poisoning and 32 patients (21.33%) had mild poisoning (see **Figure 6**). The majority of the patients had serious poisoning. Our may be partially due to the way of death, as the majority of cases in this study drank poison with the intention of killing themselves, in which case the amount consumed would have been substantially more than accidental or extremely infrequently homicidal intake.

During the 3 days that the patients were monitored, 40% of them died (including those who went into a coma), while 60% recovered with the help of treatment. 17.33% of all fatalities—or deaths—occurred within 24 hours of hospital admission (see **Figure 7**). Only 12% of patients with severe poisoning survived, and all deaths were related to it. The mortality rate for patients with suicidal organ phosphorus poisoning was reported to be 26% in a study by Kar [21], which is greater than the rate we discovered because our investigation also looked at other causes of death.

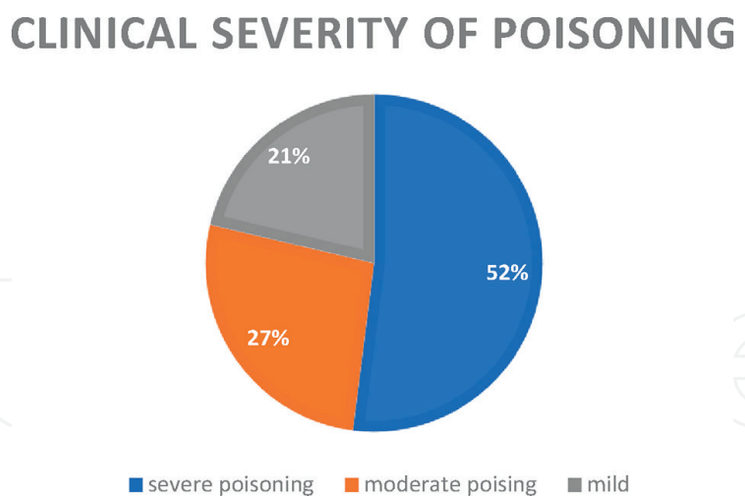

Figure 6.
Clinical severity of poisoning.

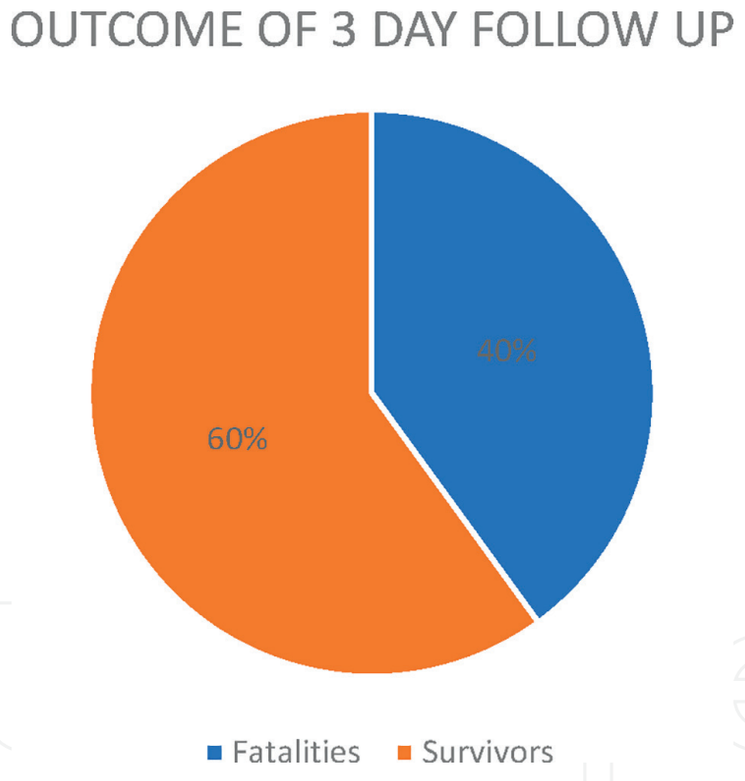

Figure 7.
Final outcome of 3 day follow-up post poisoning.

The mortality rate of 17.30 percent reported in a research by Singh et al. [16] is consistent with our 24-hour mortality rate.

Pseudocholinesterase levels in the blood (**Table 3**; **Figures 8–10**).

Plasma pseudo-cholinesterase levels, as shown in **Table 3** were compared and in the group that had experienced severe poisoning were observed to range from 912 to 2490 U/L (mean value = 1696.62 U/L and S.D. = +/− 438.99 U/L). All 60 fatalities (40%) noted in this study were included in this category. When the plasma levels of each of the 60 fatal instances were compared, it was shown that they were statistically

Clinical grade of poisoning		Plasma Pseudo-Cholinesterase Levels			Percentage suppression of Plasma Pseudocholinesterase level
		Range (U/L)	Mean (U/L)	Standard deviation (U/L)	
Severe	Death within 24 hours (17.33% mortality rate)	912 to 1678	1380	200.68	89.24 to 93.19%
	Death over a period of 3 days following admission (40% mortality rate)	912 to 2490	2158.15	774.15	84.04 to 93.19%
Moderate		4128 to 7642	5339.40	1121.33	51.01 to 69.19%
Mild		7654 to 11,230	9110.38	927.29	28.01 to 42.88%

Table 3.
Clinical grade of poisoning and its relation to plasma pseudo-cholinesterase.

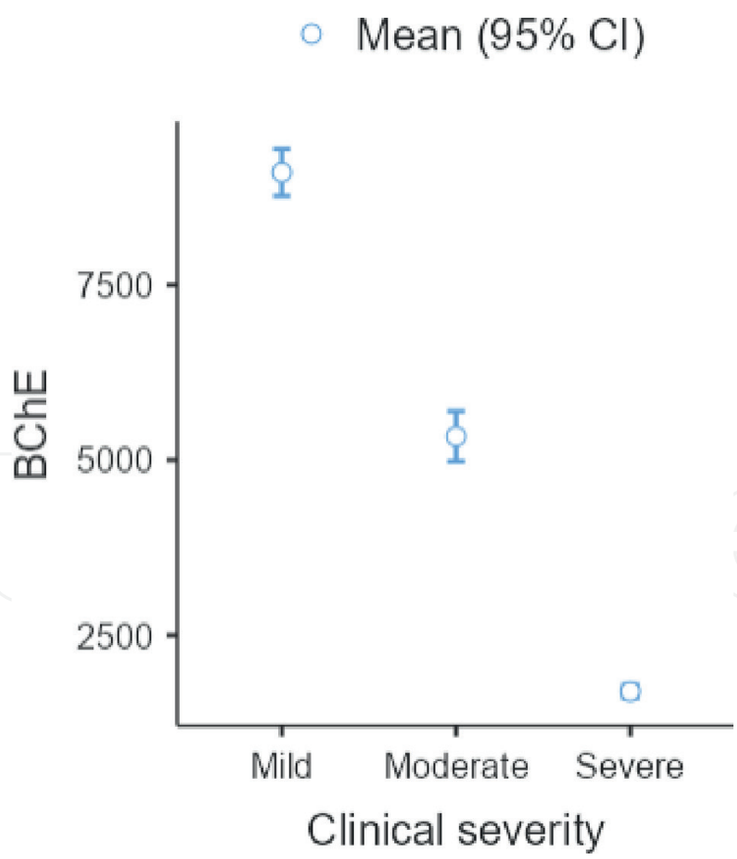

Figure 8.
Clinical severity.

very significant ($p < 0.01$). As a result, plasma pseudo-cholinesterase is suppressed by 84.04 to 93.19%. Even though 18 patients (12%) who had severe poisoning survived, there was no statistically significant difference between them and the fatalities

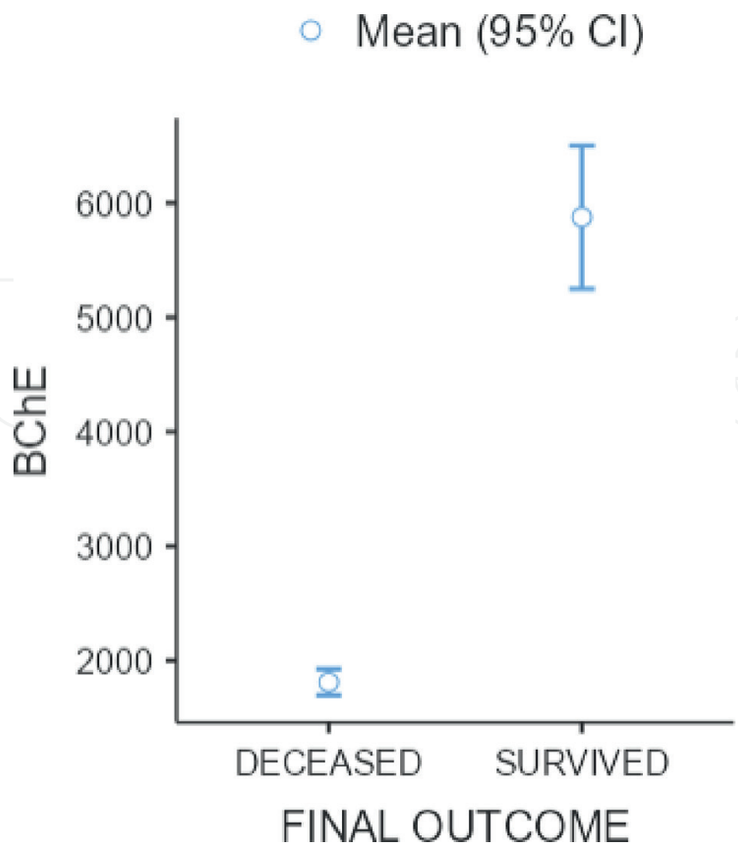

Figure 9.
Final outcome.

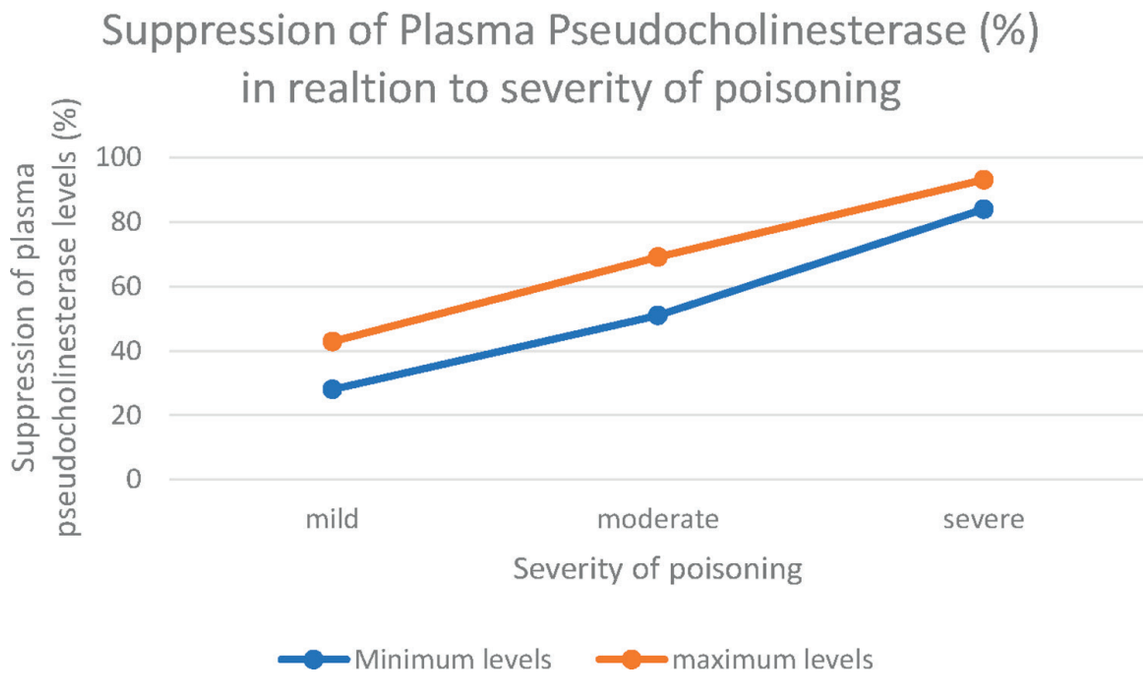

Figure 10.
Suppression of plasma pseudocholinesterase (%) in relation to severity of poisoning.

($p > 0.5$). The clinical severity also worsened with reduction in plasma pseudocholinesterase levels as depicted in **Figure 8** with correspondingly higher fatality as depicted in **Figure 9**.

The plasma-pseudocholinesterase levels were found to be statistically highly significant ($p < 0.01$) and ranged from 912 to 1678 U/L (mean value = 1390.35 U/L and S.D. = +/− 200.68 U/L), suppressing plasma pseudo-cholinesterase by 89.24 to 93.19% in the 26 patients (17.33%) who passed away within 24 hours of hospital admission.

When plasma pseudo-cholinesterase levels in the group with mild poisoning were evaluated, it was discovered that they ranged from 4128 U/L to 7642 U/L (mean value = 5339.40 U/L and S.D. = +/− 1121.33 U/L) and were statistically highly significant ($p < 0.01$). This results in a 51.01 to 69.19 percent reduction in plasma pseudo-cholinesterase.

When plasma pseudo-cholinesterase levels in the group with mild poisoning were analysed, it was discovered that they ranged from 7654 to 11,230 U/L (mean value = 9110.38 U/L and S.D. = +/− 927.29), and that this difference was statistically highly significant (p 0.001). As a result, plasma pseudo-cholinesterase is reduced by 28.01 to 42.88%.

The range of suppression of plasma pseudocholinesterase showed a linear correlation with clinical severity of poisoning as depicted in **Figure 10**.

Severe poisoning accounted for all the 60 fatalities (40%) observed in this study and only 18 patients (12%) survived. The Plasma Pseudocholinesterase levels of all the 60 fatal cases were compared with those who survived and found to be statistically highly significant ($p < 0.01$). As a result, the estimated levels of pseudocholinesterase at the time of hospital admission serve as an excellent prognostic indicator and also aid in the dose adjustment of numerous medicines used for therapy. Inhibition of plasma pseudocholinesterase from 84.04 to 93.19% was linked to severe poisoning when fatality occurred well over 3 days after hospital admission. Plasma pseudocholinesterase inhibition of 89.24 to 93.19% (as observed in patients who passed away within 24 hours of arrival) is linked with 100% mortality. This demonstrates a connection between plasma pseudocholinesterase and poisoning severity. And a fatal outcome is linked to the inhibition of this enzyme by more than 89.24% (i.e., plasma pseudocholinesterase levels below 1678 U/L). This is consistent with a research by Xu et al. [22] that found severe acute organophosphorus poisoning happens when plasma pseudocholinesterase levels approach 10%. This study's findings concur with a cohort study by Eddleston and collegues [23] who discovered that plasma pseudocholinesterase activity of 600 U/L at admission was highly specific for dimethoate toxicity and very sensitive to chlorpyrifos poisoning. According to Sunder Ram et al. [8] plasma pseudocholinesterase levels below 10% of normal are associated with a poor prognosis, which is consistent with the findings of this investigation. In acceptance with this study are studies by Reddy [1], Pillay [4] and Sozmen and collegues [24] as well. No discernible difference was seen in the levels of pseudocholinesterase in postmortem samples from brought-dead subjects and partially treated cases, according to Kukde and collegues [25].

Plasma pseudocholinesterase concentrations in mild and moderate poisoning were also found to be statistically highly significant ($p < 0.01$) and hence the observed levels can be effectively used in assessing the patient outcome and also for calibration of dose of pralidoxime which is the specific antidote.

4. Conclusion

1. Total of 150 cases were included in the present study who had organophosphate poisoning.

2. Majority of the cases belonged to age group between 21 to 30 years and the incidence among males (73%) is higher than that in females (27%).

3. All the cases were agricultural farmers by occupation.

4. Average time taken by the cases to reach hospital was 5 hours.

5. Malathion, Dimethoate and Dichlorvos were the most common poisons consumed in decreasing order.

6. Majority of the cases belonged to severe grade (52%) of poisoning presenting with coma and convulsions.

7. Malathion and parathion were associated with highest mortality (15% each).

8. Major patients (43.33%) consumed between 101 to 200 ml of the poison and most of them were in the severe group with high mortality.

9. There is a fairly good correlation between clinical severity of organophosphorus poisoning and Plasma Pseudocholinesterase levels and the plasma pseudocholinesterase levels equal to or less than 1390.35 U/L (+/− 200.68 U/L) was fatal. This amounts to suppression of plasma pseudocholinesterase by 90.414% (+/−1.384%).

Acknowledgements

I sincerely thank Dr. Bandenawaz my beloved senior and now currently Professor and Head of FMT in Navodaya Medical College Hospital & Research Center, Raichur for his constant help and encouragement during my study. His words of wisdom and timely help and support have helped me a great deal in accomplishing this study.

Conflict of interest

Nil

Notes/thanks/other declarations

Nil

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