STUDY OF ELECTROCARDIOGRAPHIC CHANGES IN ORGANOPHOSPHATE COMPOUND POISONING

Submitted By

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2011

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I hereby declare that this dissertation entitled **"Study of Electrocardiographic changes in organophosphate compound poisoning"** is a bonafide and genuine research work carried out by me under the guidance of **DR.M.S.MULIMANI** $_{\textbf{MD}}$, Professor of Medicine.

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LIST OF ABBREVATIONS

APACHE	:	Acute physiology and chronic health evaluation score
ARDS	:	Adult respiratory distress syndrome
AV	:	Atrio-ventricular
CNS	:	Central nervous system
DAM	:	Di-acetyl monoxime
ECG	:	Electrocardiograph
IV	:	Intravenous
LGB	:	Landry Guillian Barre
N.M.	:	Neuro-Muscular
OP	:	Organophosphate
PAM	:	Pralidoxime
Prolonged QT	:	Prolonged QT_c Interval
SinusT	:	Sinus tachycardia
SinusB	:	Sinus bradycardia
SCE	:	Serum cholinesterase
ST-T	:	ST segment and T wave

ABSTRACT

Background and objective :

The commonest type of insecticidal poisoning is organophosphorus poisoning. Cardiac complications that often accompany poisoning with these compounds may be serious and are often fatal. These complications are potentially preventable if they are recognized early. The present study was therefore undertaken to study the ECG changes in organophosphate poisoning.

Material and methods

50 consecutive patients presenting with OP poisoning and admitted to BLDEU's Shri B.M. PATIL Medical College from October 2008 to March 2010 were studied. History was taken, detailed clinical examination was done and relevant investigations were done. Confirmation of poisoning was done by history of poisoning, clinical features, inspection of the container and estimation of serum cholinesterase values. An ECG was taken at the time of admission and repeated when changes appeared on the cardiac monitor. An ECG was also taken prior to discharge of the patient and various changes were studied.

Results

Out of the 50 cases included in the study group, males and females were in equal number. The vulnerable age group was between 15 to 25 years. At admission, the most common ECG change was sinus tachycardia which was seen in 21 (42%) patients. ST-T changes were seen in 40% patients. Prolonged QT_C Interval (corrected for heart rate) was

seen in 18% of the patients. Sinus bradycardia was noticed in 8% patients. Arrythmias were observed in 6% patients. Mortality was seen in 6% of them.

Prior to discharge, ST-T changes were seen in 14% patients. Sinus tachycardia persisted in 6% patients and prolonged QT_C in 4% patients.

The present study shows significant correlation between prolonged QT_c and mortality (p value .001). Also, a strong correlation is observed between ST-T changes and mortality (p value .029).

Conclusion:

The most common ECG change was sinus tachycardia followed by ST-T changes. ECG alterations can be used as an index of prognosis especially with regard to sudden death. It is recommended that patients of OP poisoning having abnormal ECG changes (especially ST-T and prolonged QT) be monitored carefully till these changes revert to normal, even if clinical recovery has already occurred. This can help in reducing the mortality from poisoning.

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INTRODUCTION

In 1976, the World Health Organization (WHO) using data from 19 countries estimated that approximately 5,000,000 cases of acute pesticide poisoning were occurring annually and resulting in 9000 or more deaths, 99 % of which were in the third world countries. In 1981, the estimate was 7,50,000 cases annually, whilst in 1983 the figure was 2 million, of which 4000 were fatal.[1] The annual incidence in the year 1990 was 3 million cases.

The commonest types of insecticidal / pesticide poisoning are organophosphorus poisoning, chlorinated hydrocarbons, aluminium phosphide, carbamates and pyrethroids.[2]

The organophosphorus compounds may be inhaled or ingested accidentally or intentionally, in industries, trade, agricultural fields or homes. The first account of the synthesis of an organophosphorus compound tetra ethyl pyrophosphate (TEPP), an anti acetyl cholinesterase, was given by Clermont in 1854.

Organophosphate poisoning is primarily a problem of developing countries. It is estimated that in India about 5 – 6 persons per lakh of population die due to poisoning. The exact incidence of organophosphorus poisoning in India is uncertain due to lack of data / lack of proper reporting. Being predominantly an agricultural country, pesticides and insecticides are used abundantly for cultivation and access to these poisonous chemical substances by the population is easy. Among adults, incidence is more in females of all age groups and generally, those in second and third decades of life are more likely to be affected.

Organophosphorus compounds are anti acetylcholinesterases which exert their toxicity by interfering with the normal function of acetylcholine, an essential neuro - transmitter throughout the autonomic and central nervous system. The manifestations of toxicity are a result of this effect.

Cardiac complications that often accompany poisoning with these compounds may be serious and are often fatal. These complications are potentially preventable if they are recognized early.

Not rarely, a patient of Organophosphate poisoning dies suddenly after an initial apparently good recovery suggesting a serious myocardial electrical disturbance as the probable cause. The clinical relevance of the associated ECG changes is not yet clear.

The present study was therefore undertaken to study the ECG changes in organophosphate poisoning.

AIMS AND OBJECTIVES

OBJECTIVE OF THE STUDY:

To study the electrocardiographic changes in cases of organophosphate compound poisoning.

REVIEW OF LITERATURE

PHARMACOLOGY OF ORGANO PHOSPHORUS COMPOUNDS

OP compounds are usually esters, amides or thiol derivatives of phosphoric or phosphonic acids.

The organophosphorus compounds are irreversible anticholinesterases which combine with the enzyme cholinesterase and make them inactive. These combine with only esteratic site of cholinesterase and consequently esteratic site is phosphorylated. The hydrolysis of phosphorylated site is however slow[2].

This inhibition of acetylcholinesterase causes acetylcholine to accumulate at synaptic cleft. The Ach then acts at the cholinergic receptor sites and thus, potentially capable of producing effects equivalent to excess stimulation of cholinergic receptors throughout the central and peripheral nervous system[11].

Commercial formulations of organophosphorus insecticides may contain more than one organophosphorus compound. The biological behaviour and toxicity to man of organophosphorus compound combinations and impurities may be different from those of the single compound[7].

Pharmacokinetics

Most organophosphorus compounds are rapidly and well absorbed from the skin , mucous membrane, conjunctiva, gastro-intestinal tract and lungs. These chemicals are detoxified by cytochrome P450 mediated mono-oxygenases in liver. But some

metabolites are more toxic than parent compounds as the case in the conversion of parathion, diazinon and malathion to oxons.[9]

Table 1 : Classification of Insecticides:[7,11]

OrganoChlorine Compounds	OrganoPhosphorus Compounds	Carbamates
Methoxychlor	Chlorthion	Carbaryl
DDT	Diazinon	Pyrolan
HCH Lindane	Dioxathion	Dimetilan
Chlordene Hepatochlor	Dimethoate	Propoxur
Dieldrin	Malathion	Synthetic
Aldrin	Fenthion	Pyrethroids
	Methylparathion,	
	Parathion	
	Ronnel	
	Trichlorfos	
	Dichlorvos, Chlorpyrifos	

Table 2 : Frequently encountered organophosphorus poisonings in hospital emergencies: [7, 10]

Generic name	Trade name
Fenthion	Baytex, Lebaycid, Fenthiosul, Agrocidin
Fenitrothion	Tik-20, Folithion, Agrothion, Vikathion, Sumithion, Fenitrosul-50, Fenicol
Malathion	Finit, Vegfru Malatox, Agromal, Cythion, Kathion, Maladan, Malazene, Sulmathion, Licel
Methyl Parathion	Agrotex, Parahit, Metacid, Folidol-M, Metapar
Phorate	Dragnet, Phoratox
Methyl Oxydemeton	Knock Out, Metasystox
Quinalphos	Agroquin, Agroquinol, Bayrusil, Exalux

Table 3: Less commonly encountered organophosphorus poisonings.[7]

Generic Name	Trade Name
Dichlorvos (D.D.V.P.)	Agrovan,Bangvas, Savious, Agro 76 EC, Vapona, Vegfru, Divap, Divisol, Vapox, Nauvasul-76, Paradeep, Nuvan
Diazinon	Agroziron, Bazanon, Suzinon, Zionosul-20
Phosphomidon	Bangdon 85 WSC, Agromidon, 85 WSC, Entecron 85, Phamidon, Vimidon, Cildon, Sudon, Phosul
Chlorfenvinphos	Chlorfenvinphos, Birlane
Dimethoate	Agrodimet-30, Banggor-30EC, Cropgor-30, Parrydimate, Agromet-30EC, Hygro-30, Entogor, Paragor-30, Milgor, Vikagor, Dimethoate Klex Dimethoate, Rogor, Ramgor, Tara, Dimex, Sulgor, Paragor, Tagor
Ethion	Force, Ethion, Miticil, Dhan- unit, Vegfru Fosmite, RP-thion 50EC, Fethion, Mit 505, Ethiosul 50, RP-Thion EC
Formothion	Anthio, Accorthion
Ediphenphos	Hinosan
Chllorpyriphos	Coroban 20, Agrofas 20, Gilphos 20, hyban 20, Chlorofos 20, Ruban 20,Dursban, Tafaban

Autonomic nervous system

The portion of the nervous system which controls the visceral functions of the body is called autonomic nervous system. This helps in control of arterial pressure, gastro-intestinal motility, secretions, urinary bladder control, sweating and body temperature etc. One of the most striking characteristics of the autonomic nervous system is the rapidity and intensity with which it can change visceral function.

Autonomic nervous system centers are located in the hypothalamus, brain stem and spinal cord.

Sympathetic: Spinal cord - T1 – L1

Pre - vertebral ganglia - coeliac and hypogastric

Parasympathetic:

From central nervous system – III, VIII, IX, X cranial nerves.

Spinal cord - S2, S3 and S4 nerves.[5]

Anatomy & physiology of NM Junction

Acetylcholine:

Acetylcholine (Ach), first synthesized by BAYER in 1867, is a neurotransmitter. It was first recognized as a potent pharmacological substance by HUNT in 1906.

Acetylcholine is produced at

a) Autonomic effector sites innervated by postganglionic parasympathetic fibres.

b) Preganglionic autonomic fibres of sympathetic and parasympathetic ganglion cells and adrenal medulla.

c) Motor end-plates on skeletal muscle.

d) Certain synapses in central nervous system.

The Ach in the motor nerve terminal is synthesized in the axoplasm from choline and CoA by a process facilitated by the enzyme choline acetyl transferase. The choline necessary for this is derived from extra Cellular Fluid which is transported into the nerve terminal by a carrier mediated transport system.[5]

About 20% of Ach in nerve terminal is present as free Ach in the axoplasm and 80% is contained within the vesicles, each containing about

4-5 x 10^5 molecules of Ach.

Seperate pools or stores of Ach exist within the nerve terminal. Most of the Ach (80%) can be released by nerve impulses (the releasable pool), but some cannot (the non-releasable pool or stationary pool). The releasable pool consists of the Ach contained within the vesicles, whereas non-releasable pool is the Ach of the axoplasm. Releasable pool is often divided into immediately available and the reserve pool [5,8].

Acetylcholine acts through two receptors:

Muscarinic receptors

Muscarine is a poison from toad stools that activates only muscarinic receptors. Effector cells are stimulated by postganglionic neurons of the parasympathetic nervous system and also postganglionic cholinergic neurons of the sympathetic nervous system[5].

Nicotinic receptors

Nicotine will activate the nicotinic receptors in pre and post ganglionic neurons of both the sympathetic and parasympathetic systems and also in the membranes of skeletal muscle fibres at neuromuscular junction.[5]

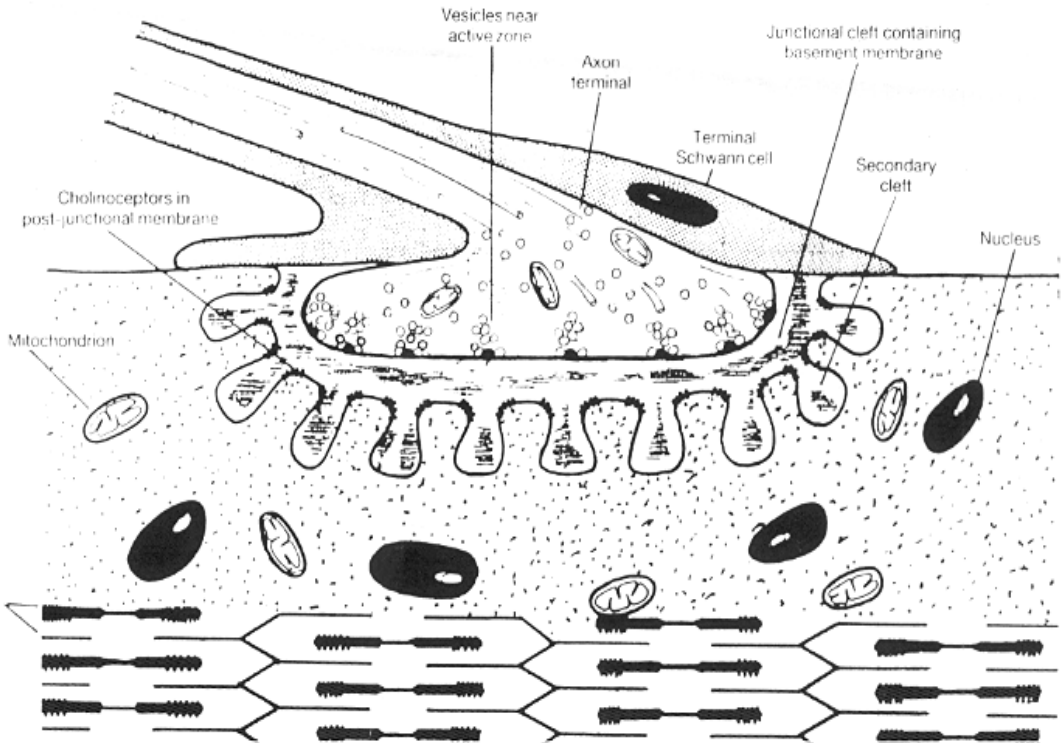


Fig 1 : Anatomy of Neuromuscular Junction – The Motor End Plate [5]

Metabolism of Acetyl choline:

Junctional acetylcholinesterase is the enzyme responsible for the hydrolysis of Ach in the synaptic cleft.

Acetyl cholinesterase is a protein attached to the basement membrane of the muscle and probably also to membranes of the motor end plates and the nerve terminals. Each molecule of the enzyme is able to bind and hydrolyze several molecules of acetylcholine. It has been estimated that for each molecule of Ach released by a nerve impulse, there are atleast 10 active enzymes sites available. This arrangement ensures that each Ach molecule only reacts once with the receptor, after which it is rapidly (in < 1msec) hydrolysed.[5,6]

Types of cholinesterase:

Two major forms of cholinesterase exist in vertebrates which hydrolyze acetyl choline[5,7]:

Plasma Cholinesterase (Pseudo or Butyryl Cholinesterase)

It is found in plasma, liver, pancreas and intestinal mucosa. (Liver being the main organ). Variations occur due to liver disease, chronic inflammation, malnutrition, morphine, codeine, succinylcholine administration and hypersensitivity reactions.

RBC Cholinesterase (True or Specific Cholinesterase)

It is found in nervous tissue, erythrocytes, Lung, spleen and grey matter. It is decreased in pernicious anemia and after anti-malarial therapy.

Acetylcholine is inactivated by combination with two sites on the enzyme RBC cholinesterase: Anionic site and Esteratic site.

Anionic Site :- Bears a negative charge which attracts the quaternary nitrogen ion of acetylcholine.

Esteratic Site :- Attracts the carboxyl group of Acetylcholine molecule and the esteratic site of the enzyme is acetylated and this results in splitting of choline. The acetyl group in combination with the esteratic site is however immediately removed as a result of combination with water, forming acetic acid. This sets the esteratic site of the enzyme free, for further inactivation of acetylcholine.[8]

Pathophysiology and Clinical Manifestations of OP Poisoning

Organophosphorus compounds are irreversible anticholinesterases and cause signs and symptoms of cholinergic excess**.**

Main actions / effects:

1. **Muscarinic** or hollow organ parasympathetic manifestations.
2. **Nicotinic** or autonomic ganglionic and somatic effects.
3. Central nervous system (**CNS**) effects.

1. **Muscarinic effects**[1,11,12]

Bronchial tree: Tightness in chest, rhinitis, dyspnoea, cough, wheezing suggestive of bronchoconstriction, increased bronchial secretions, pulmonary edema,cyanosis.

Gastrointestinal tract: Nausea, vomiting, cramps, diarrhea, tenesmus, faecal incontinence

Sweat gland: Increased sweating.

Salivary gland: Increased salivation.

Lacrimal gland: Increased lacrimation.

Cardiovascular system: Ventricular fibrillation and ventricular tachycardia

Pupils: Miosis

Ciliary body: Blurring of vision

Bladder: Frequency / urinary incontinence

2. **Nicotinic effects** [1,11,12]

Striated muscles– Muscular twitching, fasciculation, weakness, cramps and paresis including that of muscles of respiration. Acetylcholine action is for short time – 200 μ.sec.; Hence first single wave of depolarisation occurs, then rest of Ach is taken up by vesicles or destroyed by cholinesterases. But because of persistent stimulation this synchrony is lost, leading to asynchronous excitation, which causes fibrillation of muscle fibres later leading to paresis.

Sympathetic ganglia – pallor, tachycardia, increased BP.

3. **Central nervous system** [1,12]

Giddiness, tension, anxiety, restlessness, emotional lability, excessive dreaming, insomnia, headache, tremor, depression, drowsiness, confusion, slurred speech, generalized weakness, coma with absence of reflexes , type I paralysis, Cheyne' Stokes respiration, convulsions, depression of respiratory and circulatory centers with dyspnoea, cyanosis and fall in Blood pressure.[1,12]

CLINICAL EFFECTS OF OP COMPOUNDS :

Portal of entry: Oral, skin, Inhalation .

Odour :

Garlic like odour but the organic solvents which are used to mix organophosphorus compounds may mask it and in fact may smell of kerosene.[2,7]

Eye:

Miosis is a characteristic sign found in many patients with severe and moderately severe poisoning, but it is not invariably present. Mydriasis can also be seen. Fear, anger, pain and some other emotional stimuli are known to cause dilation of the pupil due to excessive stimulation of the sympathetic nervous system. Regardless of the mechanism, the size of pupil is subject to numerous influences and it would appear unwise to regard pupillary status alone as essential for diagnosis or as important for measuring the success of treatment.[13]

Respiratory system

Respiratory arrest, a common terminal manifestation of Organophosphorus poisoning is produced by overstimulation of receptors at three levels.

1. It can be recalled that Muscarinic action produces increased bronchial secretions, rhinorrhoea, bronchospasm and laryngospasm, which can result in airway obstruction.[15]

2. On other hand, Nicotinic effects are associated with paralysis of the respiratory muscles. Weakness of the muscles of the tongue and pharynx aggravate the upper airway obstruction.[15]

3. Finally there may be Central depression of respiration leading to cessation of breathing. This is due to direct action of the organophosphate at the cholinergic synapses in the brain stem that are involved in the control of respiration. Thomas Chang Yao Tsao et. al. observed that the cardiovascular collapse was due to depression of the circulatory centre or due to profound hypoxemia, hypercapnia and acidemia from respiratory failure.[15] Goswamy R et. al. found miosis, unconsciousness, fasciculations and low plasma cholinesterase level to be of greatest predictive value for ventilatory support.[3]

Gastrointestinal system

After ingestion of Organophosphorus compounds, the initial symptoms may be gastro intestinal, of which increased salivation, nausea, vomiting, abdominal tightness, cramps and diarrhoea are the commonest.[36,38]

Central nervous system

After human intoxication by Organophosphorus compounds, 4 varieties of neurotoxic effects have been observed:

A. Type I Paralysis, described by Wadia, are indicative of acute neurotoxic effects during the cholinergic phase of poisoning. Patients present with giddiness, uneasiness, restlessness, anxiety and tremulousness followed by headache, ataxia, drowsiness, fasciculation, mental confusion and slurred speech.[16]

Fasciculations may be influenced / modified by many factors:

1. The depressed serumcholinesterase levels from the start (to a level just critical for the physiology of neuro muscular junction).
2. Blood flow, acid base balance may influence the effect of excess acetylcholine on the neuro muscular junction.
3. A higher daily dosage of atropine may prevent fasciculations. Signs like impaired consciousness, fasciculations and miosis presenting on admission, will all respond to atropine therapy.

B. Type II Paralysis, described by Wadia and referred by Senanayake as Intermediate syndrome occurs 24-96 hours (after poisoning with Organophosphorus compounds) following the acute stage of cholinergic crisis. 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 paralysis.[16,18,35]

There are several postulations regarding the mechanism of Type II paralysis:

1. Wadia et al[16] has suggested that persistence of nicotinic effects due to lack of early use of oximes may be responsible for the paralysis.
2. However, in Senanayake series all patients had been treated with PAM and atropine. Recently, Wadia has suggested that the nicotinic effects of the Organophosphorus compounds for some reason appear later than the muscarinic effects, producing the paralysis. He also observed a low serum cholinesterase

level in serum at the time of admission in almost all cases that developed paralysis.[16,18]

3. Godath and Fisher attributed the late onset of paralysis to the release of Organophosphorus compounds from the adipose tissue acting on the nicotinic receptors.[19]

4. Delayed Polyneuropathy, described by Senanayake, seems uncommon in India, manifest after a latent period of 2-3 weeks following the acute poisoning. The polyneuropathy is predominantly distal, affecting lower limbs before the upper limbs are affected. Paraesthesias are present and muscle wasting is seen. Electrophysiological studies reveal evidence of denervation. Delayed neurotoxicity is a two step phenomenon. First step is the phosphorylation of the protein neurotoxic esterase (NTE), normally present in nervous tissue. Second step is 'ageing' of the phosphorylated enzyme complex. A high level of inhibition (70-80%) of the NTE is possibly necessary for the neurotoxicity.[20]

Table 4 : Comparison of Intermediate Syndrome and Delayed neuropathy

	Intermediate Syndrome	**Delayed neuropathy**
Latent period	1-4 days	2-3 week
Site of weakness	Proximal	Distal
Neck muscles	Affected	Not affected
Cranial nerves	Affected	Not affected
Respiratory muscles	Affected	Not affected
Electromyogram	Tetanic fade	Denervation
Recovery	4-18 days	6-12 months
OP agents commonly involved	Fenthion Dimethoate Monocrotophos	Methamidophos Trichlorphos Leptophos

d. Landry – Guillian Barre syndrome: The last variety of neurotoxicity seen is the Landry – Guillian Barre (LGB) syndrome . It has all classical features of LGB (Clinical, CSF and EMG findings) minus the presence of any other antecedent event. But the prognosis is good in the syndrome seen after exposure to organophosphorus compounds.[21]

Criteria for diagnosis of severe grade of organophosphorus poisoning:[25,27,40]

- Unconsciousness
- Marked miosis
- Loss of pupillary reflex to light
- Muscular fasciculation
- Flaccid paralysis
- Excessive secretions from mouth and nose
- Crepitations
- Respiratory distress

Rebound phenomenon [33,34]

It is often observed that cases which apparently recover in terms of level of consciousness and pulmonary edema fall back into a terminal phase. This has been attributed to toxic myocarditis and intestinal reabsorption of organophosphorus compounds .Compounds can remain bound to fat or adipose tissue for a long time and their sudden release result in rebound phenomenon. The cause of release is:

1. The continuing absorption of the toxin after the transient effect of oximes has subsided and

2. Early reduction of atropine dosage when serum cholinesterase depression is still present.

Cardiac and ECG manifestations

Cardiac complications often occur after poisoning with these compounds, which may be serious and often fatal. These complications are potentially preventable if recognized in time and treated promptly.

The current knowledge of cardiac effects of organophosphates is not voluminous and consists of limited publications. Hence many physicians may not be fully aware of these complications. This fact magnifies the importance of acquiring knowledge related to these manifestations.

There are various cardiac manifestations of OP poisoning. According to Ludomirsky et al[42] , three phases of cardiac toxicity can be described:

1. A brief initial period of hypertension and sinus tachycardia.

These are considered nicotinic effects and may be due to a pheochromocytoma-like pattern caused by excessive release of catecholamines from the adrenal medulla which is under sympathetic control.

2. A prolonged phase characterised by sinus bradycardia and hypotension.

These effects are due to extreme parasympathetic overactivity, usually accompanied by electrocardiographic ST-T segment changes and AV conduction disturbances of varying degrees. The clinical significance of these findings is usually related to the severity of intoxication.

3. A phase of QT prolongation, polymorphic tachycardia and sudden cardiac death.

The third phase can occur a few hours after the intoxication, but sometimes it may occur 1 to 15 days following exposure to the OP, when the signs of clinical intoxication have already subsided. It is possible that with nerve agents, this period is even longer. Late arrythmias are imminent even if the treatment in the acute phase is efficient [49,50].

S B Agarwal[43] et al described various ECG changes in OP poisoning. Sinus tachycardia (24%) was the most common abnormality followed by depression of ST segment and inversion of T wave (7.4%) and sinus bradycardia (6.6%).

P Karki[45] et al studied cardiac manifestations of OP poisoning and stated that cardiac complications usually occur during the first hour after exposure. Sinus tachycardia (40%) was described as the most common ECG change. Prolonged QT interval , sinus bradycardia , ST-T changes, prolonged P-R interval, atrial fibrillation, ventricular tachycardia and extra systole were also described.

Mathur A[46] et al studied 150 patients of OP poisoning and described sinus tachycardia, ST elevation and depression as the most commonly encountered changes.

Dalvi C P[47] et al correlated ECG changes in OP poisoning with prognosis. ECG changes occurred more often in patients with severe intoxication. ST-T changes and low voltage changes were especially found to be related to poor prognosis. The dose of atropine required was the highest and the rate of normalisation of ECG and clinical recovery slowest, in the group with severe poisoning.

On the other hand, other ECG abnormalities like ectopic beats, conduction defects and peaked P waves returned to normal with clinical recovery and did not correlate with prognosis[51].

Irrespective of the mechanism behind ECG alterations, they can be used as an index of prognosis especially with regard to sudden death. It is recommended that patients of OP poisoning having a combination of abnormal ST-T changes and reduced voltage on their ECG be monitored carefully till these changes revert to normal, even if clinical recovery has already occurred. With such monitoring, fall in mortality from 20% to 4.1% has been reported.[47]

Other ECG changes in OP poisoning cases, which included intraventricular conduction delays during the acute phase and prolonged ST-T wave changes which correlated in severe fatal cases with histological signs of diffuse myocardial damage.[48]

The role of estimation of serum cholinesterase :

Estimation of acetyl cholinesterase level in circulation is theoretically preferred in organophosphorus poisoning since it would reflect the degree of inhibition of synaptic cholinesterase at motor end plates. But, in practice, estimation of serum cholinesterase has an advantage because the measurement is simpler and more accurate than estimation of the acetylcholinesterase. Serum cholinesterase levels can indicate the prior presence of cholinesterase inhibition even after recovery of acetylcholinesterase activity by pralidoxime in organophosphorus poisoning.[12]

In acute poisoning, manifestations generally occur only after more than 50% of cholinesterase is inhibited. The severity of manifestation parallels the degree of inhibition of serum cholinesterase (SCE) activity pertinently only in initial stages.[12]

The normal values range between 5100 to 11700 IU / Ltr. According to Proudfoot,[22] the organophosphorus poisoning may be classified based on the levels of serum cholinesterase (SCE) on presentation as follows :

- In mild poisoning: SCE level is 20 - 50 % of normal
- In moderate poisoning: SCE level is 10 - 20 % of normal
- In severe poisoning: SCE level is < 10 % of normal

In severe poisoning, return of normal levels requires above 4 weeks for serumcholinesterase and about 10 to 12 weeks for acetylcholinesterase.

Acetylcholinesterase regenerates at approximately 1% per day, whereas serum cholinesterase regenerates at a more rapid rate, at approximately 25% in the first 7-10 days.[23,24] The confirmation of diagnosis depends on demonstrating reduced cholinesterase activity in the circulating blood.[26,30]

Activity is expressed as percentage of normality of healthy adults. Values above 80% normality imply that no significant absorption has taken place. There is no specific upper limit, cases with values between 50% and 80% are usually symptomless but indicate a slight absorption. Early effects, mainly abdominal discomfort and cold sweats may occur at 20% - 30% of normality. Severe cases would be expected to have very low serum cholinesterase activity in the blood, for example 5-10% but some apparently severe cases of parathion poisoning have had upto 50% normal values, while some cases of over exposure, with serum cholinesterase levels reduced to 5 % normality, have proved symptomless[1].

Changes in acetylcholinesterase levels during poisoning and treatment :

Serum cholinesterase inhibition depends on the concentration of the inhibitor, as this is subject to continuous unknown fluctuations and it is not possible to predict the time course of inhibition.[30] Enzyme inhibition will proceed until a steady state is reached and spontaneous reactivation is achieved.[31,32]

Cholinesterase activity of red blood cells is instantly and completely restored and long lasting, but the return of activity of serum cholinesterase (SCE) is transient and variable after oximes. The main effect produced by the administration of oximes is the restoration of the true acetylcholinesterase activity & prompt and complete relief of symptoms, especially after alkylphosphate poisoning. True cholinesterase level indicates effectiveness and serum cholinesterase levels indicate the prior presence of cholinesterase inhibitor.[12]

Molly J Coye et a [26] followed up three groups of agricultural workers exposed to organophosphorus pesticides , in the absence of baseline values for cholinesterases. They found that both red cell and serum cholinesterase values were decreased during the follow up period. They also confirmed that in the absence of baseline values, interpretation of single post exposure value is not useful because of the wide range of normal cholinesterase activity and advised sequential estimations to be better indicators.

Semir Nouira et al [28] estimated serum cholinesterase levels at the time of admission after acute organophosphorus poisoning with the aim to determine whether this has got a prognostic value with reference to severity, treatment, APACHE scoring and need for ventilation. They found no correlation between serum cholinesterase levels and Organophosphorus poisoning as per the above assessments.

However, A.Ramani et.al., [29] studied 25 cases of organophosphorus poisoning and found a good prognostic value for serum cholinesterase from samples drawn at regular intervals.

Disadvantages of serum cholinesterase estimation:

1. Normal values of serum cholinesterase are widely variable from one person to another as well as in the same individual at different times.[32]
2. Low serum cholinesterase levels have been observed in some disease states and may also be genetically determined.
3. Following pralidoxime administration, true cholinesterase levels indicate the effectiveness of PAM and serum cholinesterase levels indicates prior presence of cholinesterase inhibition even after recovery of true cholinesterase activity by PAM, hence the latter cannot be used to assess the effectiveness of PAM therapy.[31]
4. Serum cholinesterase level at a particular time in the blood is not constant but continuously changing as the inhibition of the enzyme by inhibitors and spontaneous reactivation will take place simultaneously.[32]

Diagnosis of organo-phosphorus poisoning:[23,24]

1. History or evidence of exposure to organophosphorus compounds
2. Symptoms and Signs of poisoning
3. Effect of pralidoxime and atropine
4. Inhibition of the cholinesterase activity in the blood

MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING:[7,23,37,39]

1.Supportive measures:

Oral suction of secretions

Maintenance of circulation

Establishment of respiration

2. Prevention of absorption:

Decontamination

Emesis

Adsorbant

Cathartics

Bowel wash

3 .Specific chemotherapy:

Atropine

Oximes

Treatment of complications

1. Supportive measures:

It should be ensured that upper airway is not blocked and throat secretions should be intermittently sucked to avoid aspiration. Respiratory insufficiency is the commonest cause of death. Hence, positive pressure ventilation should be given if patient develops signs of respiratory failure.

2. Prevention of absorption:

a. Decontamination:

Contaminated clothing should be changed, skin should be washed.

b. Emesis:

Unless the patient is comatosed, convulsing or has lost the gag reflex emesis should be initiated. Should these contraindications be present, endotracheal intubation should precede gastric lavage with wide bore tube.

c. Adsorbant:

Activated charcoal functions as an adsorbant and should be given within 3 hours of ingestion and if gastric emptying is delayed it may be useful for upto 12 hours after ingestion. It is the most valuable single agent for emergency management of oral drug poisoning.

d. Cathartics:

Cathartics function by decreasing absorption and increasing elimination. It should be administered as early as possible because relapse is thought to be due to delayed absorption.

e. Bowel wash :

To be done twice a day which helps to remove toxic substance from large bowel.

Specific therapy:

1. **Atropine**: It is an alkaloid derived from a plant Atropa belladona and Datura stramonium. Atropine acts as a physiological antidote, effectively antagonising the muscarinic receptor- mediated actions of organophosphorus agents. Dose of atropine should be sufficient to produce signs of atropinisation. Size of the pupil is a good indicator for regulating the dose of atropine.[13]

Pharmacological action:

At autonomic ganglia where transmission mainly involves nicotinic receptors, atropine produces partial blockade at high doses. Atropine does not inhibit the nicotinic actions of acetylcholine. To some extent it inhibits the central effects produced by these compounds. Thus, atropine antagonises mainly the muscarinic effects of organophosphorus poisoning. Atropine is partially detoxified in the liver and partly excreted unchanged in the kidney.

Dosage:

In order to prevent pulmonary edema, early prompt atropinisation is important. Severe poisoning may require heavy doses, upto 100 mg over first 24 hours to achieve adequate atropinisation. Atropinisation should be maintained till absorbed organophosphate is fully metabolised which may require 2 - 200 mg or more of atropine over a few hours to several days. Abrupt withdrawal can cause pulmonary edema.[33,34]

Signs of atropinisation:

Pupillary dilatation cannot be taken as an indication of atropinisation since Organophosphorus Compounds can produce both miosis or mydriasis. Pupils becoming initially pin point later becoming dilated is a reliable sign of atropinisation. Since tachycardia and bradycardia can occur, tachycardia (130 – 140/min.) cannot be a reliable sign. Other signs include flushing, dry skin and dry mouth. Full atropinisation is indicated by clearing of rales and drying of pulmonary secretions.[33,34]

Adverse effects:

Dry mouth, hot dry skin, thirst, flushing, fixed dilated pupil, tachycardia, impaired speech, tremor, coma, convulsions, respiratory failure and collapse. Potential fatal dose is 25-30 mg/kg body wt.

2. Oximes:

DOSAGE[22,23] : Pralidoxime - 1 gm IV followed by 500 mg/ 6th hrly for 2 more days.

Obidoxime - 3-6 mg / kg IV over 5-10min.

D.A.M. (Diacetyl Monoxime) -1-2 gm IV slowly at 200 mg / min to be repeated after 20 min.

Pralidoxime chloride is given at a dose of 1gm IV for adults over a period of 15-30 min. A dose of 30 mg/kg IV at a rate not exceeding 500 mg every 4 hours for first 24 hours is also advocated.

The IV administration of PAM usually produces slight to moderate reversal of plasma and red cell cholinesterase inhibition but has no effect on the gastrointestinal symptoms, tachycardia, sweating, salivation or on CNS symptoms produced by anticholinesterase compounds.[37,39]

Enzyme reactivation occurs most markedly at the neuromuscular junction with rapid improvement of skeletal muscle response. An important effect of this action is normalisation of diaphragmatic excursion and respiratory effort. To be effective, oximes should be given within 36 hours of poisoning, after which it becomes ineffective by a process called 'ageing'. Phosphorylated cholinesterase undergoes ageing and the aged enzyme is resistant to oxime action and cannot be reactivated.[1,23]

Oximes are effective in severe cases of poisoning presenting with pulmonary edema, muscular twitching, muscle weakness and respiratory paralysis. Prompt recovery of consciousness by many patients indicate that it has a definitive CNS effect in 10- 15 min. In clinical practice, even 2 or 3 days after onset of poisoning, Oximes might be useful probably because newly inhibited cholinesterase is constantly produced as a result of the continuing absorption of organophosphorus compounds from the GIT or other tissue.

Pralidoxime is preferable since it is more soluble and produces fewer side effects. When given in large doses at the proper time, PAM antagonises the CNS effect of organophosphorus compounds.[1,23] Grob found that oximes diminished necessity for or duration of artificial ventilation.[24]

Adverse effects:

In higher doses, oximes can inhibit cholinesterase enzyme and they can cause neuromuscular blockade. If infused rapidly they can cause weakness, drowsiness, giddiness, blurred vision, diplopia, headache, nausea, tachycardia and hypotension.[40,41]

3.Treatment of complications :

Seizures, Pulmonary edema, Pneumonia, Adult respiratory distress syndrome (ARDS), Renal failure, Hypotension / shock, arrhythmias, etc. are all managed as per standard protocol.[37,39]

Recommendations for management of cardiac manifestations[44]

1. A baseline ECG should be performed in all OP intoxicated patients.
2. ECG changes should be observed regularly on the cardiac monitor.
3. Patients should not be discharged before ECG normalisation, even if clinical recovery has occurred.
4. A holter test is recommended prior to discharge of patients who had QT prolongation.
5. In cases of mass casualty where technical factors prevent the application of the recommendations, special attention should be paid to patients with severe intoxication and those who had arrythmias or marked ST-T changes.

MATERIALS AND METHODS

Source of data:

50 consecutive patients presenting with OP poisoning and admitted to BLDEU's Shri B.M. PATIL Medical College from October 2008 to March 2010 .

Sample size:

With incidence rate of ECG changes in acute OP poisoning as 62 % (ref. Singapore medical journal 2004; 45(8) : 385 – 389) and allowable error of 25 %, with 95 % confidence level ,the calculated sample size is 50.

$$N = \frac{(1.96)^2\, pq}{L^2}$$

Statistical method

a) Diagrammatic representations

b) Proper statistical tests i.e. chi square test.

Method of collection of data

The study will be carried out on patients admitted with a provisional diagnosis of OP poisoning made on the basis of a definite history of OP poisoning by patient or attendants in BLDEU's Shri B.M.Patil Medical College Hospital and Research Center, Bijapur.

Inclusion criteria

All patients with definite history of OP poisoning substantiated by examination of the container when available, further substantiated by –

1. Typical clinical features(hypersalivation, miosis and fasciculations)
2. Estimation of serum cholinesterase levels

Exclusion criteria

a) Patients with known cardiac disease

b) Patients with chronic lung disease

c) Patients with prior ECG abnormalities, if known

OBSERVATIONS AND RESULTS

Of the total 97 consecutive patients admitted to Shri B.M.Patil Medical College and Hospital during the study period i.e. from October 2008 to March 2010, 50 were included in the study group on the basis of the inclusion criteria including retrieval of the container and compound name further substantiated by typical clinical features (hypersalivation, miosis and fasciculations) and estimation of serum cholinesterase levels.

Rest were excluded in accordance with the exclusion criteria , namely patients with known cardiac disease, patients with chronic lung disease and patients with prior known ECG abnormalities.

This study comprised 50 patients, out of which 25 were males and 25 females. The most common age group affected was 15-25 years (60%) followed by the age group of 26-35 years (28%). Least commonly affected were the age groups of 46-55 years(2%) and above 55 years(2%)

As per concerned occupation , majority were farmers(40%), followed by housewives (26%).

Clinically , increased secretions, miosis and fasciculations were the predominant manifestations in this study. Pain abdomen and vomiting were present in all the cases.

The commonest organophosphorus compound encountered was Monocrotophos (16%) and Malathion (16%) followed by Dimethoate (12%)

No deviations from normal values were observed in hematological examination of all the patients. Amongst biochemical investigations, random blood sugar was high in 10% of patients at the time of admission, but none turned out be diabetic at the time of discharge.

Chest X-ray was evident of pulmonary edema in 4 patients at the time of admission of which all 4 patients required assisted ventilation. Aspiration pneumonia was seen in 3 patients out of the total 50.

No biochemical abnormality concerned to Renal and Hepatic system were seen in study group.

The commonest complication encountered was respiratory failure , necessitating ventilator support in 11 out of the 50 patients (22%).

A 12 lead Electrocardiogram was recorded at the time of admission and repeated subsequently when changes were seen on the cardiac monitor. A final ECG was taken prior to discharge of the patient.

At admission, the most common ECG change was sinus tachycardia which was seen in 21 (42%) patients. Out of these 21, 14 were males.

The next most common change observed was ST-T changes which was seen in 20 out of the total 50 patients (40%). Out of these, 10 were males. The ST-T changes included elevation or depression of the ST segment and flattening, inversion or peaking of the T wave.

Prolonged QT_C Interval (corrected for heart rate) was seen in 9 out of the 50 (18%) patients, out of which 6 were males.

Sinus bradycardia was noticed in 4 out of the total 50 patients, all of which were males.

Arrythmias were observed in 3 out of the total 50 (6%) patients. There were 2 males out of these 3.

Out of the total 50 patients, mortality was seen in 3 (6%) of them. All these patients were on ventilator. In these 3 cases, the last ECG recording prior to death was studied.

Prior to discharge, most common persisting ECG change was ST-T change which was seen in 7 (14%) patients. Sinus tachycardia persisted in 3 (6%) patients and prolonged QT_C in 2 (4%) patients.

Table 5 : Distribution of study subjects according to age

Age in years	Frequency	Percentage
15-25	30	60
26-35	14	28
36-45	4	8
46-55	1	2
>55	1	2
Total	50	100

Graph 1

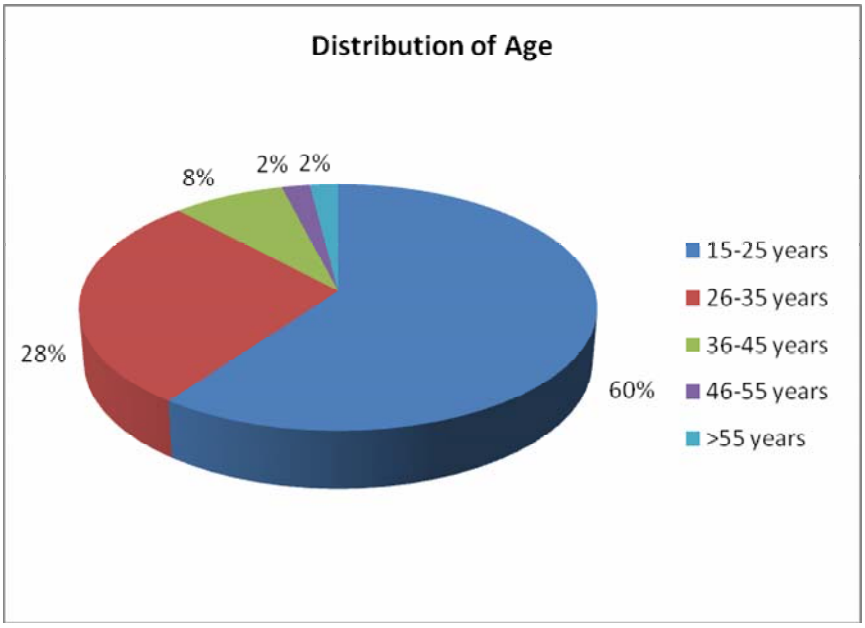


Table 6 : Distribution of study subjects according to sex

Sex	Frequency	Percentage
Male	25	50
Female	25	50
Total	50	100

Graph 2

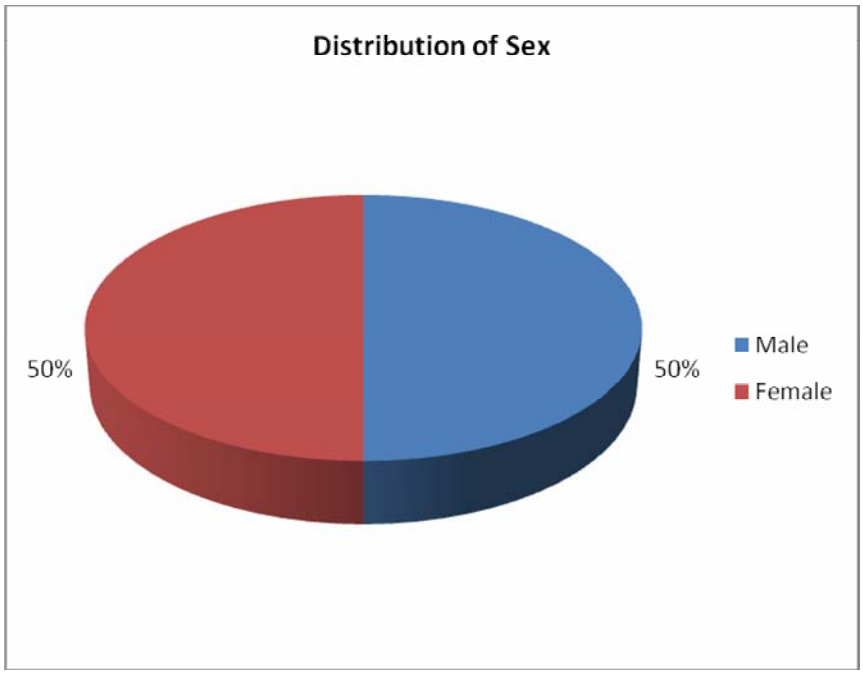


Table 7 : Distribution of Occupations

	Male		Female		Total	
Occupations	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Farmer	18	72	2	8	20	40
Labourer	1	4	4	16	5	10
Students	1	4	6	24	7	14
Housekeeper	0	0	13	52	13	26
Shopkeeper	3	12	0	0	3	6
Driver	2	8	0	0	2	4

Graph 3

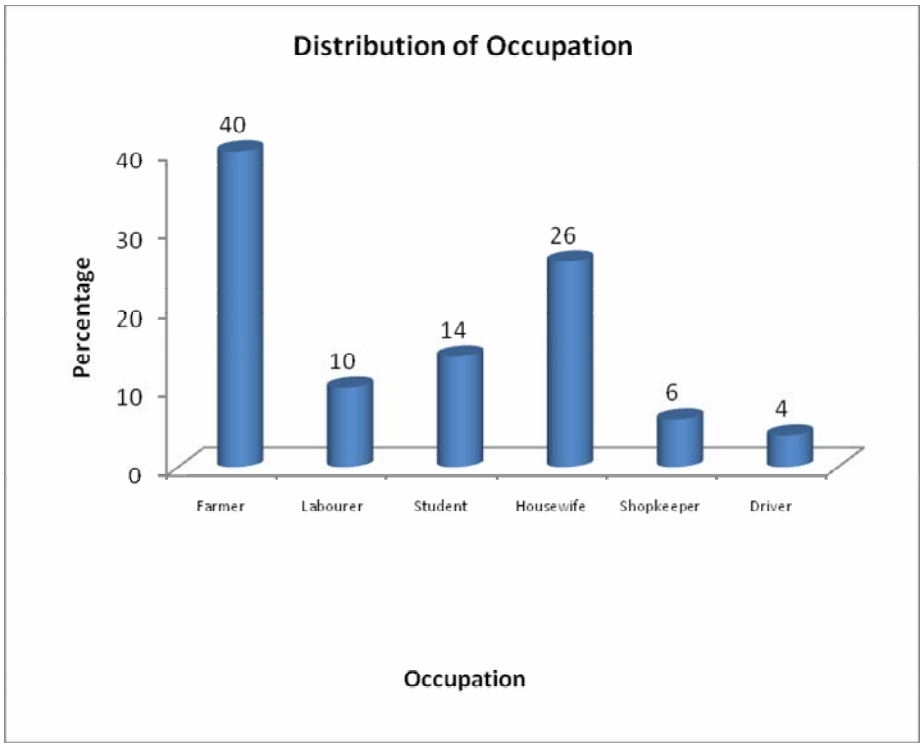


Table 8: Distribution of Compound type

Compound	Frequency	Percentage
Dimethoate	7	14
Monocrotophos	8	16
Ethion	8	16
Malathion	6	12
Parathion	3	6
Chlorpyriphos	1	2
Fenthion	2	4
Quinalphos	5	10
Dichlorvos	4	8
Chlorfenvinphos	3	6
Fornothion	3	6
Total	50	100

Graph 4

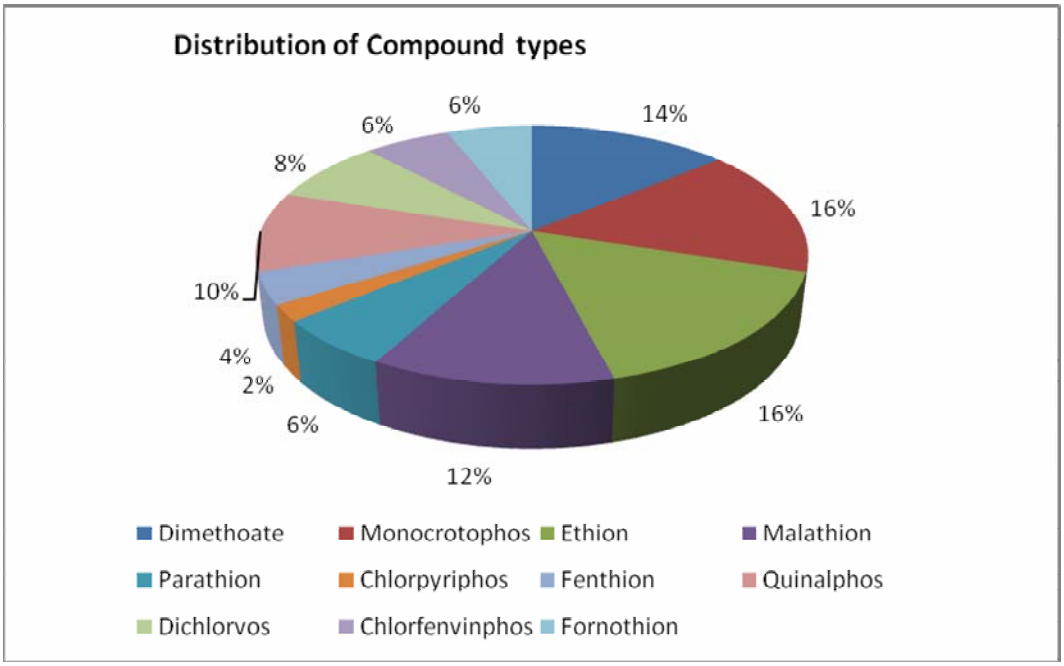


Table 9 : Distribution of Serum Cholinesterase

	Male		Female		Total	
Serum Cholinesterase	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
100-400	5	20	4	16	9	18
401-800	8	32	9	36	17	34
801-1200	9	36	8	32	17	34
1201-1600	0	0	4	16	4	8
1601-2000	3	12	0	0	3	6

Graph 5

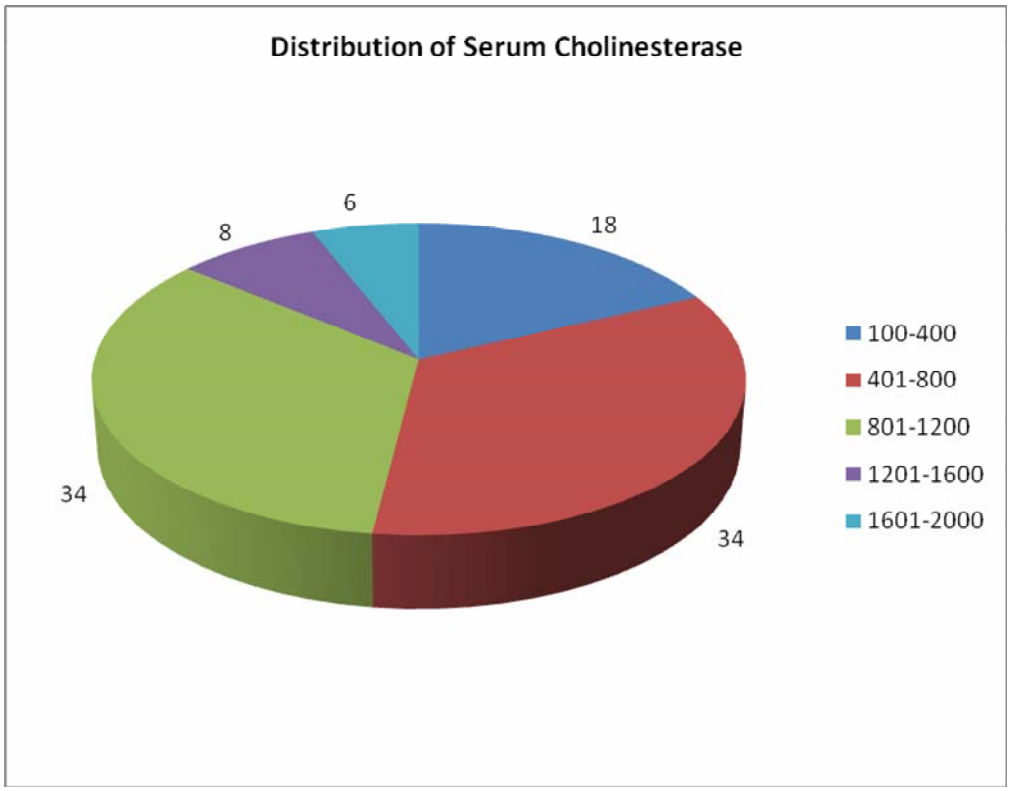
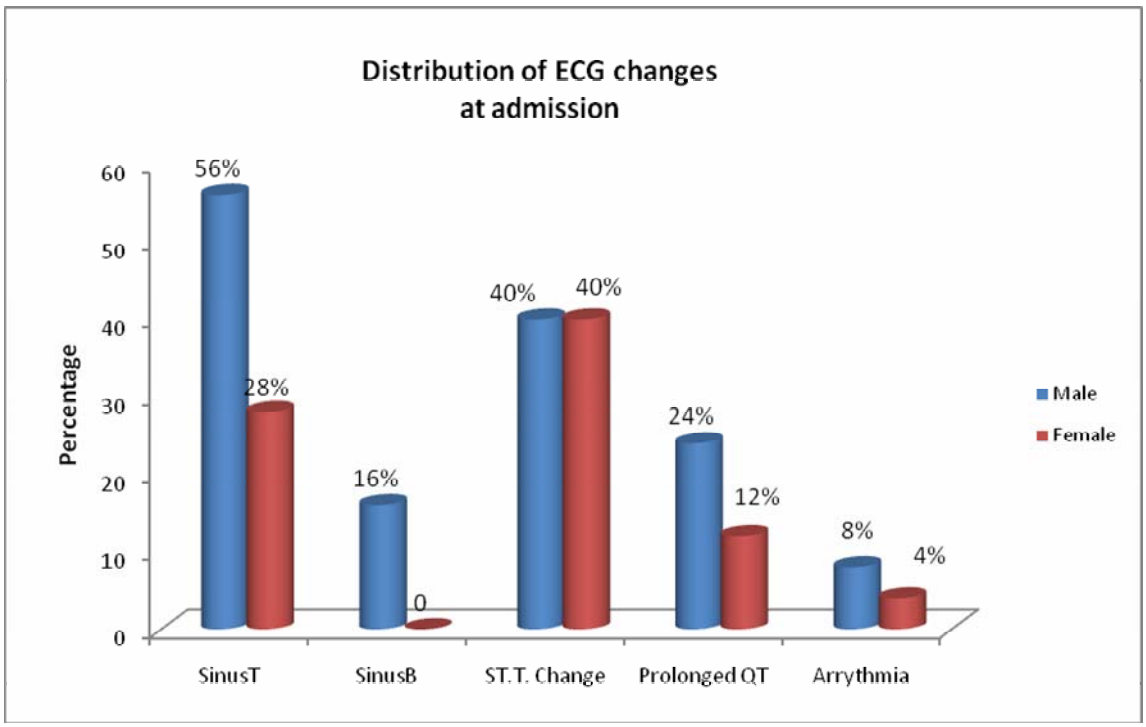


Table 10: Distribution of ECG Changes at admission

OP Poisoning	Male	Female	Total
Sinus tachycardia	14 (56%)	7(28%)	21(42%)
Sinus bradycardia	4(16%)	0	4(8%)
ST-T changes	10(40%)	10(40%)	20(40%)
Prolonged QT_c	6(24%)	3(12%)	9(18%)
Arrythmia	2(8%)	1(4%)	3(6%)

Graph 6 (a)



Graph 6 (b)

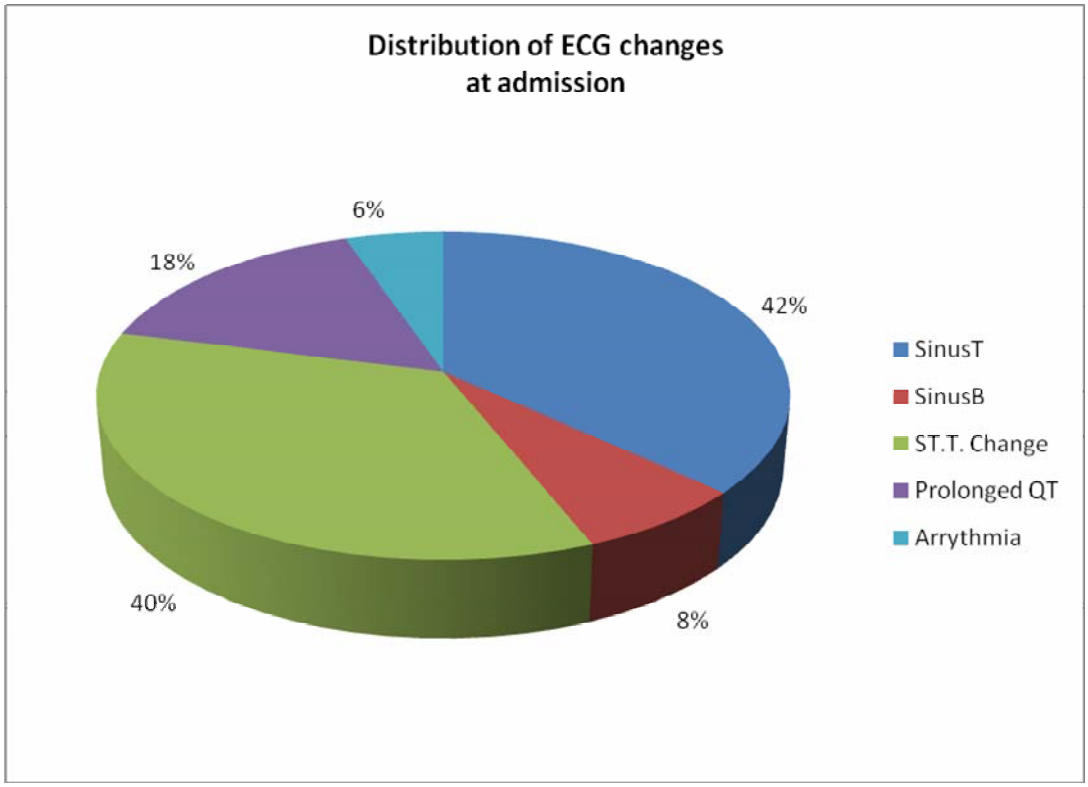
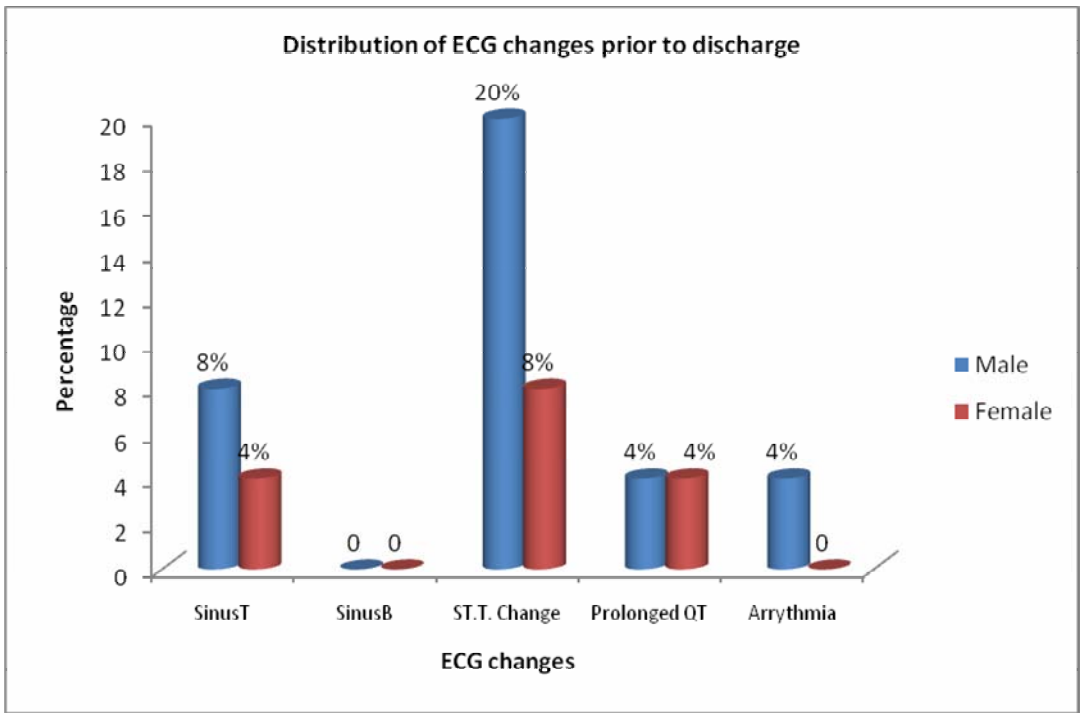

Distribution of ECG changes at admission
6%
18%
42%
40%
8%
SinusT
SinusB
ST.T. Change
Prolonged QT
Arrythmia

Table 11: Distribution of ECG changes prior to discharge

OP Poisoning	Male	Female	Total
Sinus tachycardia	2(8%)	1(4%)	3(6%)
Sinus bradycardia	0	0	0
ST-T changes	5(20%)	2(8%)	7(14%)
Prolonged QT_c	1(4%)	1(4%)	2(4%)
Arrythmia	1(4%)	0	1(2%)

Graph 7 (a)



Graph 7 (b)

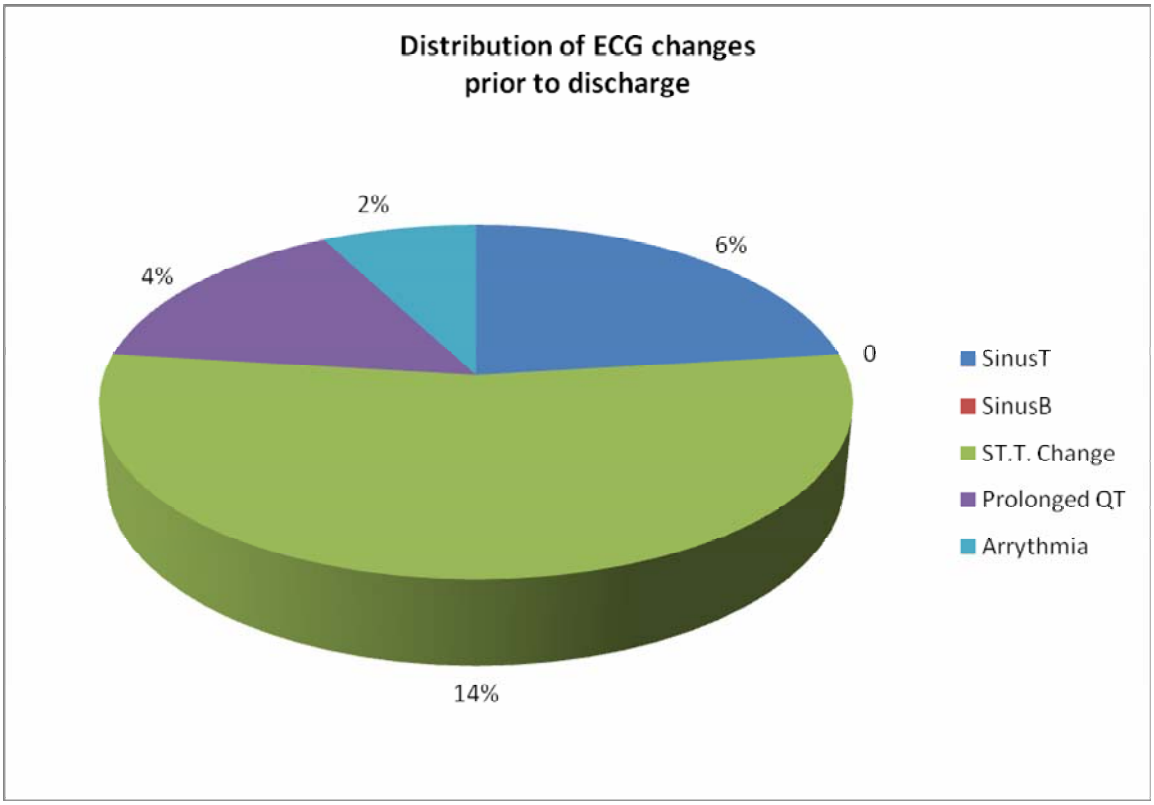

Distribution of ECG changes
prior to discharge
2%
6%
4%
0
14%
SinusT
SinusB
ST.T. Change
Prolonged QT
Arrythmia

Table 12 : Association of mortality with Sinus tachycardia

			MORTALITY		Total
			No	Yes	
Sinus tachycardia	No	Count	29	0	29
		Percentage	100%	0%	100%
	Yes	Count	18	3	21
		Percentage	85.7%	14.3%	100%
Total		Count	47	3	50
		Percentage	94%	6%	100%

P value = 0.036 (significant)

Graph 8

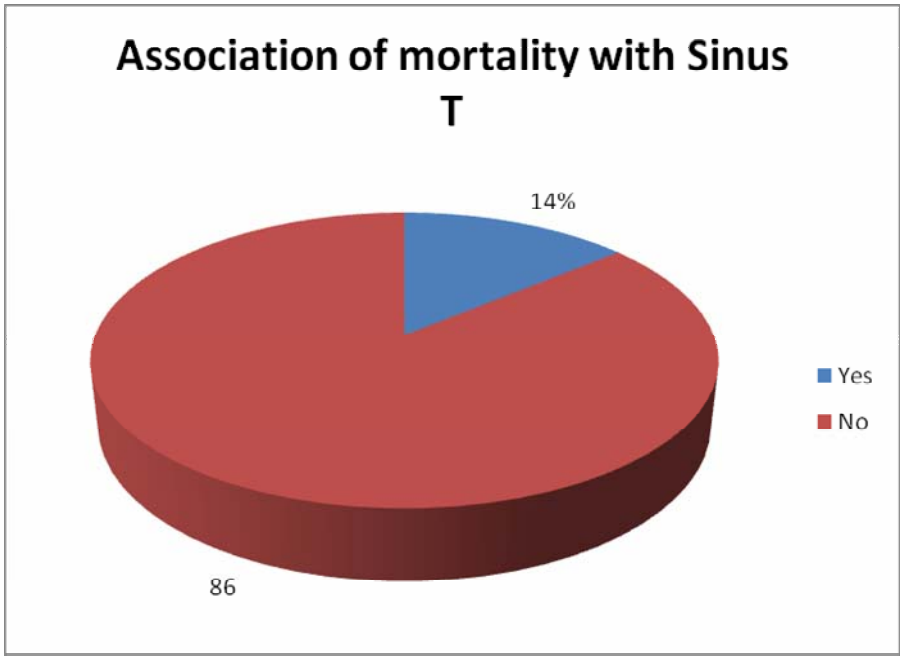


Table 13 Association of mortality with ST-T changes

			MORTALITY		Total
			No	Yes	
ST-T Changes	No	Count	30	0	30
		Percentage	100%	0%	100%
	Yes	Count	17	3	20
		Percentage	85%	15%	100%
Total		Count	47	3	50
		Percentage	94%	6%	100%

P value = 0.029 (significant)

Graph 9

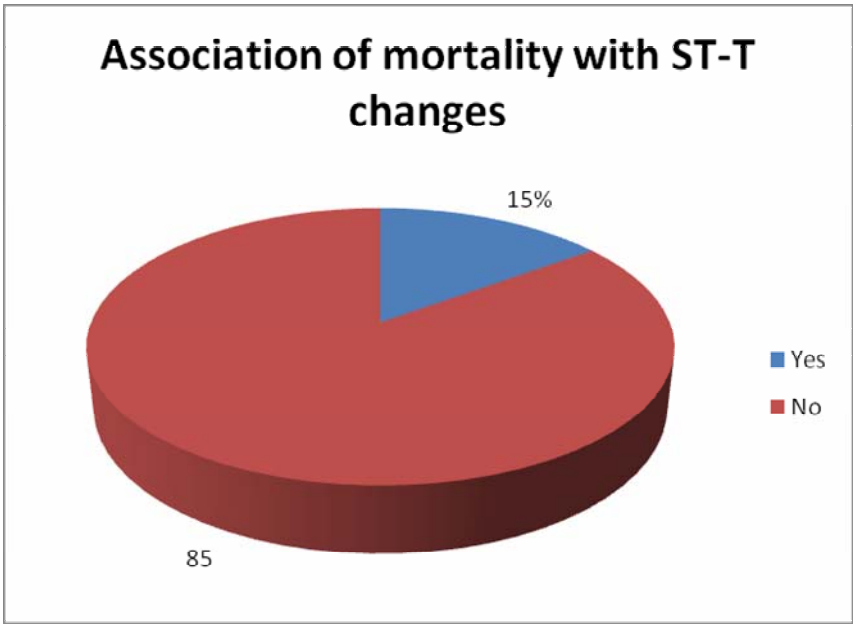


Table 14 Association of mortality with Prolonged QT_c

			MORTALITY		Total
			No	Yes	
Prolonged QT_c	No	Count	41	0	41
		Percentage	100%	0%	100%
	Yes	Count	6	3	9
		Percentage	66.7%	33.3%	100%
Total		Count	47	3	50
		Percentage	94%	6%	100%

P value = 0.001 (significant)

Graph 10

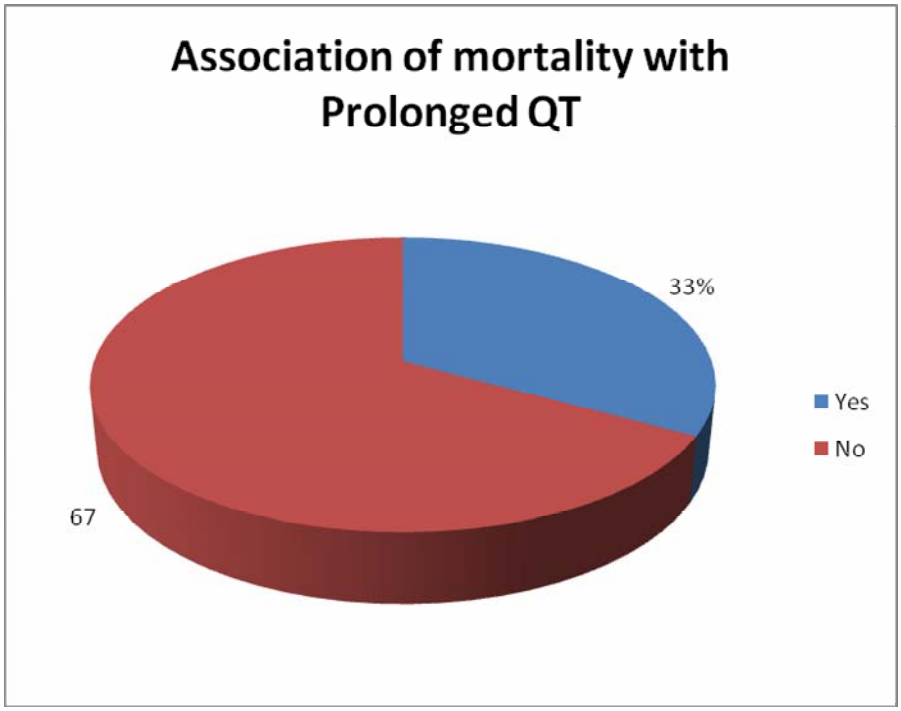


Table 15 : Association of mortality with Sinus Bradycardia

			MORTALITY		
			No	Yes	Total
Sinus Bradycardia	No	Count	43	3	46
		Percentage	93.5%	6.5%	100%
	Yes	Count	4	0	4
		Percentage	100%	0%	100%
Total		Count	47	3	50
		Percentage	94%	6%	100%

P value = 0.598

Table 16 : Association of mortality with Arrythmia

			MORTALITY		
			No	Yes	Total
Arrythmia	No	Count	44	3	47
		Percentage	93.6%	6.4%	100%
	Yes	Count	3	0	3
		Percentage	100%	0%	100%
Total		Count	47	3	50
		Percentage	94%	6%	100%

P value = 0.652

DISCUSSION

Of the various agents used for suicidal attempts in India, organophosphorus compound form a significant group. Organophosphorus insecticides are highly toxic to humans. Poisoning due to organophosphorus insecticides is steadily increasing in India. These pesticides are preferred for the purpose of suicide due to their easy availability and potent toxicity.

When we look at the age distribution of the cases in our study, an incidence of 88% was noted in 15 to 35 years age group. The age group 15 to 35 years is the most critical period because this is when one is likely to face various problems that may lead to psychological stress and ultimately force a person to take drastic steps to end his life by consuming available poisons. Goel et al[25] reported an incidence of 86.4% of cases including second and third decade.

In the present study, males and females are in equal proportions. Mehta et al[30](1971) and Goel et al[25](1998) reported higher proportion of male patients.

Among the organophosphorus compounds, Tik – 20 (2% Fenitrothion) was of choice in the study reported by Agarwal S.B.[43] Monocrotophos was organophosphorus compound of choice in study by Goel et al[25]. In our study Monocrotophos (16%),Ethion (16%) and Dimethoate (14%) were commonly used

Ventilatory support requirement specially with dimethoate was more in the present study which is similar to Goel et al[25] study.

Clinically vomiting, pain abdomen ,altered sensorium, hypersalivation, breathlessness were common symptoms in this study. Clinical signs like miosis, pungent odor, tachycardia, signs of respiratory insufficiency, fasciculations and altered sensorium were common in our study. Agarwal S.B. (1991)[43] and Goel et al 1998 [25] also observed similar clinical scenario in their studies.

The commonest complication encountered was respiratory failure , necessitating ventilator support in 11 out of the 50 patients (22%).

A 12 lead Electrocardiogram was recorded at the time of admission and repeated subsequently when changes were seen on the cardiac monitor. A final ECG was taken prior to discharge of the patient.

At admission, the most common ECG change was sinus tachycardia which was seen in 21 (42%) patients. S B Agarwal[43] et al described various ECG changes in OP poisoning. Sinus tachycardia (24%) was the most common abnormality.

P Karki[45] et al studied cardiac manifestations of OP poisoning and stated that cardiac complications usually occur during the first hour after exposure. Sinus tachycardia (40%) was described as the most common ECG change. Mathur A[46] et al studied 150 patients of OP poisoning and described sinus tachycardia as the most commonly encountered change.

In the present study, ST-T changes were seen in 20 out of the total 50 patients (40%). P Karki[45] et al noticed ST-T changes in 29.7 % cases while Mathur A[46] et al have described ST-T changes in 46.66% of the cases.

Prolonged QT_C Interval (corrected for heart rate) was seen in 9 out of the 50 (18%) patients. P Karki[45] et al has described prolonged QT_c Interval in 37.8% of the cases in his study.

Sinus bradycardia was noticed in 4 out of the total 50 patients. Arrythmias were observed in 3 out of the total 50 (6%) patients. P Karki[45] et al noticed sinus bradycardia in 18.9% cases and arrhythmia in 16.2% of the cases in his study group. S B Agarwal[43] et al has described sinus bradycardia in 6.6% of the cases in his study.

There are various cardiac manifestations of OP poisoning. According to Ludomirsky et al[42] , three phases of cardiac toxicity can be described:

1. A brief initial period of hypertension and sinus tachycardia
2. A prolonged phase characterised by sinus bradycardia and hypotension.
3. A phase of QT prolongation, polymorphic tachycardia and sudden cardiac death.

Dalvi C P[47] et al correlated ECG changes in OP poisoning with prognosis. ECG changes occurred more often in patients with severe intoxication. ST-T changes and low voltage changes were especially found to be related to poor prognosis. In the present study, out of the total 50 patients, mortality was seen in 3 (6%) of them. All the 3 cases had ST-T changes at the time of admission. Also, the ST-T changes persisted in 1 out of these 3 cases prior to death.

In the present study, out of the 3 mortalities ; 2 had prolonged QT_c Interval at admission and the prolongation persisted in 1 of the case prior to death. Out of the total 50 cases, prolonged QT_C was seen in 9 patients. Lyzhnikov EA[49] et al studied 183 cases

of OP poisoning, out of which 34 patients had prolonged QT_C Interval. Out of these 34, 29 patients died.

According to Bar Meir[44] et al, prolonged QT_c Interval is associated with higher chances of arrhythmia and sudden cardiac death.

The present study shows significant correlation between prolonged QT_c and mortality (p value .001) Also, a strong correlation is observed between ST-T changes and mortality (p value .029)

SUMMARY

A prospective study of 50 cases of OP poisoning with regard to their ECG changes between October 2008 to March 2010 has been reported.

Epidemiological factors like age, sex, occupation, nature of poisoning and population distribution are discussed. A detailed analysis is carried out based on clinical features, type of compound, nature of poisoning and requirement of assisted ventilation in all patients.

Lastly the various ECG changes in organophosphorus compound poisoning and their relation with mortality has been discussed.

From the present study the following conclusion are drawn

Out of the 50 cases included in the study group, males and females were in equal number.

The vulnerable age group was between 15 to 25 years (60%). Farmers (40%) and House wives (26%) were common. Monocrotophos, Ethion and Dimethoate were common culprits.Vomiting and pain abdomen were common symptoms while miosis, fasciculations and increased secretions were common signs.

Confirmation of poisoning was done by history of poisoning, clinical features, inspection of the container and estimation of serum cholinesterase values.

At admission, the most common ECG change was sinus tachycardia which was seen in 21 (42%) patients.

ST-T changes were seen in 40% patients. Prolonged QT_C Interval (corrected for heart rate) was seen in 18% of the patients. Sinus bradycardia was noticed in 8% patients. Arrythmias were observed in 6% patients. Mortality was seen in 6% of them. All these patients were on ventilator.

Prior to discharge, ST-T changes were seen in 14% patients. Sinus tachycardia persisted in 6% patients and prolonged QT_C in 4% patients.

The present study shows significant correlation between prolonged QT_c and mortality (p value .001) Also, a strong correlation is observed between ST-T changes and mortality (p value .029)

CONCLUSION

Organophosphorus compounds are commonly used agents for suicidal purpose because of their easy availability.

These compounds are reversible inhibitors of cholinesterase. The common mode of death is due to respiratory failure which requires ventilator support.

Cardiac complications often occurs which may be serious and often fatal. These complications are potentially preventable if recognized in time and treated promptly.

ECG alterations can be used as an index of prognosis especially with regard to sudden death. It is recommended that patients of OP poisoning having abnormal ECG changes (especially ST-T and prolonged QT) be monitored carefully till these changes revert to normal, even if clinical recovery has already occurred. This can help in reducing the mortality from poisoning.

BIBLIOGRAPHY

1. Karalliadde L, Senanayake N : Organophosphorus insecticide poisoning Br. J. Anaesthesia. 1989; 63 : 736-750.
2. Narayan Reddy KS : The Essentials of Forensic Medicine and Toxicology. 23rd Edition : 415-417.
3. Goswamy R et al : Study of Respiratory Failure in Organophosphorus and Carbamate poisoning Heart Lung 1994; 23 (6): 466-472.
4. Aygun D et al : Serum Acetylcholinesterase and Prognosis of Acute Organophosphorus poisoning J. Toxicol 2002; 40 (7): 903-910.
5. Guyton : Text book of Medical Physiology 8th Edition ; 80-83.
6. Aitkenhead AR : Text book of Anaesthesia 5th Edition ; 90-92.
7. Casarett & Doull : Toxicology 7th Edition ; 888-893.
8. Clarke RS, Fee JP : Anaesthetic Physiology and Pharmacology 1st Edition.
9. Bennet PN : Clinical Pharmacology 9th Edition ; 436-438.
10. Gordon HA, Shaprio S : Forensic medicine - A guide to principles 3rd edition ; 204-221.
11. Goodman and Gilman : The Pharmacological basis of therapeutics 10th Edition ; 179-184.
12. Tatsuji Namba et al : Poisoning due to organophosphate insecticides. American Journal of Medicine 1971; 50: 475 – 492.
13. Dixon EM et al : Dilatation of the pupils in Parathion poisoning JAMA 1957 ; 163 : 444 -445.

14. API Text book of Medicine 8th edition ; 1492-1493.

15. Thomas Chang–Yao Tsao et al : Respiratory failure of acute organophosphate and Carbamate poisoning CHEST 1990;98(3) : 631-636.

16. Wadia RS et al : Neurological manifestations of organophosphate insecticide poisioning. Journal of Neurology ,Neurosurgery and psychiatry 1974 ; 37 : 841-847.

17. Samal KK, Sahu CS: Organophosphorus poisoning and Intermediate neurotoxic syndrome. JAPI 1990 ; 38:181 – 182.

18. Karalliedde L, Senanayake N: Acute organophosphorus insecticide poisoning. A Review Ceylon Medical Journal 1986;31: 93-100.

19. Natan Gadoth, Allan Fisher : Late onset of neuromuscular block in organophosphorous poisioning. Annals of internal medicine 1978 ; 88 : 654 – 655.

20. Karalliedde L , Senanayake N : Acute organophosphorus poisoning in Sri Lanka . Forensic Science International 1988 ; 38 : 97-100.

21. Mishra VN, Raman PG : Guillian Barre Syndrome as a sequela of organophosphorus poisoning . JAPI 1988 ; 36 : 347-49.

22. Proudfoot A : Organophosphate and carbamate insecticides in diagnosis and management of Acute poisoning 1st Edition Oxford Blackwell Scientific 1982 ;153 – 7.

23. Namba T. : Diagnosis and treatment of O.P poisoning Medical times 1972; 100 : 100 – 120.

24. Grob D Koelle GB : Hand book of experimental pharmacology. 1963 ; 989 – 1027.

25. A Goel et al : Organophosphate poisoning : Predicting the need for ventilatory support JAPI 1998 vol 46 ; 9 : 786 – 790.

26. Jolly J Coye et al : Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses. Arch intern Med 1987;147 :438 – 442.

27. Lee P ,Tai DY: Clinical features of patients with acute organophosphate poisoning requiring intensive care . Intensive care medicine 2001 ; 27(4) : 694 – 699.

28. Semir Nouira et al : Prognostic value of serum cholinesterase in organophosphate poisoning . CHEST 1994 ; 106 : 1811 – 1814.

29. Ramani et al : Serum cholinesterase levels as a indicator of prognosis in organophosphorus poisoning . JAPI 1988 ; 36 : 23 – 24.

30. Mehta AB et al : Clinical features and plasma acetylcholinesterase activity in poisoning with insecticidal organophosphorus compounds. Singapore. Med J *1971*; 12 : 80-85.

31. Suvit Areekul et al : Serum and red cell cholinesterase activity in people exposed to organophosphate insecticide. South east Asian Journal TROP. MED. PUB. HLTH 1981 ; 12 : 94 – 95.

32. A.Dua et al : Serum cholinesterase levels in organophosphorus poisoning- does it Predict Mortality? JAPI 2001; 49: 168 – 169.

33. Avasthi G ,Singh G : Serial Neuro- electrophysiological studies in acute organophosphate poisoning - correlation with clinical findings, serum cholinesterase levels and atropine dosage. JAPI 2000 ; 48 ; 794 – 799.

34. J .Sunder Ram et al : Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning . JAPI 1991 ; 39 : 190 – 193 .

35. DeBleecker JL: Intermediate Syndrome in Organophosphate poisoning: An overview of experimental and clinical observation. J. Toxicol Clin. Toxica 1995; 683-686.

36. Bardin PG, Van Eaden SF, Moolman JA: Organophosphate Poisoning and Carbamate poisoning. Arch Interna Med. 1994 ; 154 : 1433 – 1441.

37. Bardin PG, Van Eaden SF, Joubert JP: Intensive Care management of acute Organophosphate Poisoning: S Afr. Med. J, 1987 ; 72 : 593 – 597.

38. Karki P, Hansdak SG, Bhundari S, Shukla A, Koirala S.A clinicoepidemiological study of organophosphorus poisoning at a ruralbased teaching hospital of eastern Nepal. Trop Doct 2001; 31: 32-4.

39. Dutoit PW, Maller FO, Ventonder WM, Ungerer MJ: Experiencewith intensive care management of organophosphate insecticide poisoning. S Afr Med J 1981; 60: 227-9.

40. Hayes MM, Van der Westhuizen NG, Gelfand M. Organophosphate poisoning in Rhodesia. A study of the clinical features and management of 105 patients. S Afr Med J 1978 ; 54 : 230-4.

41. Durham WF, Hayes WJ. Organic phosphorus poisoning and its therapy. Arch Environ Health 1962; 5 : 24.

42. Ludomirsky A, Klein H, Sarelli P, Becker B, Hoffman S, Taitelman U. Q-T prolongation and polymorphic (torsade de pointes) ventricular arrhythmias

associated with organophsphorus insecticide\poisoning. Am J Cardiol 1982; 49: 1654-8

43. Agarwal SB, Bhatnagar VK, Agarwal A et al. Impairment in clinical indices in acute organophosphate poisoning patients in India. The Internet Journal of Toxicology.2007; 4(1) : 1-8.

44. Bar Meir, Eran, Schein et al. Guidelines for treating cardiac manifestations of OP poisoning. Critical Reviews in Toxicology 2007; 1 : 1-8.

45. Karki P, Ansari JA, Bhandary S, Koirala S. Cardiac and ECG manifestations of acute organophosphate poisoning. Singapore Medical Journal 2004; 45(8): 385-389.

46. Mathur A,Swaroop A,Agarwal A. ECG changes in acute OP and aluminium phosphide poisoning. The Indian Practitioner 1999 April; 52(4) : 249-252.

47. Dalvi CP,Abraham PP,Iyer SS.Correlation of ECG changes with prognosis in OP poisoning. Journal of Postgraduate Medicine 1986; 32(3): 115-119.

48. Chharba M L,Sepaha G G,Jain S R et al. ECG and necrosy changes in OP compound poisoning. Indian Journal of Medical Science 1970; 24(7): 424-429.

49. Lyzhnikov EA, Savina AS, Shepelev VM. Pathogenesis of disorders of cardiac rhythm and conductivity in acute organophosphate insecticide poisoning. Kardiologia 1975; 15 : 126-9.

50. Kiss Z, Fazekas T. Arrhythmias in organophosphate poisonings. Acta Cardiol 1979; 34: 323-30.

51. Saadeh AM, Farsakh NA, Al-Ali MK : Cardiac manifestations of acute carbamate and organophosphate poisoning. Heart 1997; 77 : 461-4.

BLDEU'S SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR

STUDY OF ECG CHANGES IN OP POISONING

PROFORMA

Name:	IP. No:
Age:	Address:
Sex:	Date of Admission:
Occupation:	Date of Discharge:
Religion:	Status at Discharge:

PRESENTING COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

Time of exposure to OP compound

Mode of exposure

PAST HISTORY:

PERSONAL HISTORY:

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION:

Pallor
Icterus
Cyanosis
Clubbing
Pedal edema
Lymphadenopathy

Vital Signs:

Pulse rate
Blood pressure
Temperature
Respiratory rate

SIGNS OF OP POISONING

A. MUSCARINIC MANIFESTATIONS

Miosis
Rhonchi
Crepitations
Dyspnoea
Increased sweating/salivation/lacrimation

B. NICOTINIC MANIFESTATIONS

Fasciculations
Cramps
Weakness
Areflexia
Hypertension
Mydriasis
Tachycardia

C. CNS MANIFESTATIONS

Restlessness

Emotional lability

Drowsiness

Confusion

Slurred speech
Ataxia
Coma
Convulsions

D. ODOUR

SYSTEMIC EXAMINATION

GASTROINTESTINAL SYSTEM

Inspection

Palpation

Percussion

Auscultation

CARDIOVASCULAR SYSTEM

Inspection

Palpation

Percussion

Auscultation

RESPIRATORY SYSTEM

Inspection

Palpation

Percussion

Auscultation

CENTRAL NERVOUS SYSTEM :

Higher mental functions

Cranial nerves

Motor system

Sensory system

Signs of meningeal irritation

PROVISIONAL DIAGNOSIS :

INVESTIGATIONS

A. BLOOD

Haemoglobin

Total Count

Differential Count

ESR

B. URINE

Albumin

Sugar

Microscopy

C. BIOCHEMISTRY

Random blood sugar

Serum cholinesterase

Sodium

Potassium

Creatinine

D. 12 lead ECG

FINAL DIAGNOSIS

TREATMENT

SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTER, BIJAPUR – 586103.

CONSENT FORM

TITLE OF RESEARCH : STUDY OF ECG CHANGES IN ORGANOPHOSPHORUS COMPOUND POISONING

GUIDE : DR. M.S. Mulimani

P.G. STUDENT : DR. Aveg Bhandari

Purpose of research:

I have been informed that the purpose of this study is to study the ECG changes in OP poisoning..

Procedure:

I understand that I will undergo detailed history and clinical examination. Also,ECG will be taken and blood will be collected & sent to the laboratory for investigations.

Risks and discomforts:

I understand that there is no risk involved and I may experience mild pain during the collection of blood.

Benefits :

I understand that my participation in this study will help in recognition of existence of relationship between ECG changes and OP poisoning that will ultimately benefit my fellow beings.

Confidentiality:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

Request for more information:

I understand that I may ask for more information about the study at any time.

Refusal or withdrawal of participation:

I understand that my participation is voluntary and I may refuse to participate or withdraw for study at any time.

Injury statement:

I understand in the unlikely event of injury to me during the study I will get medical treatment but no further compensations.

(Signature of Guardian) (Signature of patient)

(If the patient is conscious,well oriented)

KEY TO MASTER CHART

IP	:	Inpatient number
Yr.	:	Years
M	:	Male
F	:	Female
Y	:	Yes/Present
N	:	No/Absent
SCE (IU/L)	:	Serum cholinesterase in international units per litre
SinusT	:	Sinus tachycardia
SinusB	:	Sinus bradycardia
ST-T	:	ST segment and T wave
Prolonged QT	:	Prolonged QT_c Interval

MASTER CHART

Sl. No.	NAME	AGE(in yr.)	SEX	OCCUPATION	IP	COMPOUND	INCREASED SECRETIONS	FASCICULATION	MIOSIS	SCE (IU/L)	AT ADMISSION			
											SINUS T	SINUS B	ST-T CHANGES	PROLONGED QT
1	Kashinath	22	M	Farmer	10706	Dimethoate	Y	Y	Y	1091	Y	N	Y	N
2	Shantawwa	27	F	Housewife	2491	Monocrotophos	Y	Y	Y	749	N	N	Y	N
3	Bhirappa	28	M	Farmer	2427	Ethion	Y	Y	Y	982	Y	N	Y	Y
4	Sangamma	21	F	Labourer	2473	Malathion	Y	Y	Y	285	N	N	Y	N
5	Sangappa	22	M	Farmer	1998	Dimethoate	Y	Y	Y	1615	Y	N	Y	Y
6	Shantamma	16	F	Farmer	3054	Dimethoate	Y	Y	Y	454	Y	N	Y	N
7	Shreedevi	16	F	Student	3019	Quinalphos	Y	Y	Y	1152	N	N	N	N
8	Shaila	18	F	Farmer	3073	Dimethoate	Y	Y	Y	1431	Y	N	Y	Y
9	Shobha	26	F	Labourer	2798	Monocrotophos	Y	Y	Y	769	Y	N	Y	Y
10	Parsappa	31	M	Farmer	2134	Parathion	Y	Y	Y	218	Y	N	Y	Y
11	Kallappa	30	M	Labourer	7633	Ethion	Y	Y	Y	335	Y	N	N	N
12	Ravi	21	M	Farmer	7693	Chlorpyriphos	Y	Y	Y	786	N	N	N	N
13	Vidyashree	18	F	Student	7981	Fenthion	Y	Y	Y	934	N	N	N	N
14	Iranna	30	M	Farmer	11039	Quinalphos	Y	Y	Y	1021	N	Y	N	N
15	Pundik	25	M	Shopkeeper	10592	Malathion	Y	Y	Y	738	N	Y	N	N
16	Rekha	26	F	Housewife	10417	Dichlorvos	Y	Y	Y	684	N	N	N	N
17	Sharanappa	19	M	Student	10386	Ethion	Y	Y	Y	387	N	N	N	N
18	Parsappa	35	M	Farmer	10163	Chlorfenvinphos	Y	Y	Y	893	Y	N	N	N
19	Iramma	30	F	Housewife	9571	Fornothion	Y	Y	Y	1127	N	N	N	N
20	Veena	17	F	Student	9534	Ethion	Y	Y	Y	693	N	N	Y	N
21	Rajbaxa	22	M	Farmer	410	Malathion	Y	Y	Y	432	Y	N	Y	N
22	Sujatha	18	F	Student	10172	Malathion	Y	Y	Y	128	Y	N	Y	N
23	Renuka	25	F	Housewife	9360	Fenitrothion	Y	Y	Y	712	N	N	N	N
24	Shreedevi	16	F	Student	9186	Dichlorvos	Y	Y	Y	664	N	N	N	N
25	Parsappa	24	M	Farmer	9004	Quinalphos	Y	Y	Y	913	Y	N	N	N
26	Hashimpeer	30	M	Shopkeeper	8800	Monocrotophos	Y	Y	Y	787	N	Y	N	Y
27	Parvati	36	F	Housewife	8776	Ethion	Y	Y	Y	1092	N	N	N	N
28	Hayyasidda	45	M	Shopkeeper	8334	Dimethoate	Y	Y	Y	458	Y	N	N	N
29	Sumangla	20	F	Housewife	8390	Malathion	Y	Y	Y	659	N	N	N	N
30	Bandu	25	M	Farmer	8140	Parathion	Y	Y	Y	948	N	N	N	N
31	Sangappa	24	M	Farmer	7957	Dichlorvos	Y	Y	Y	473	N	N	N	N
32	Sidappa	50	M	Farmer	7585	Chlorfenvinphos	Y	Y	Y	868	N	Y	N	N
33	Shivakumaar	40	M	Driver	572	Ethion	Y	Y	Y	1912	N	N	N	N
34	Ravatappa	70	M	Farmer	5547	Monocrotophos	Y	Y	Y	845	Y	N	Y	N
35	Shantappa	25	M	Driver	9372	Dimethoate	Y	Y	Y	157	Y	N	Y	N
36	Mohneesh	25	M	Farmer	5112	Monocrotophos	Y	Y	Y	635	Y	N	Y	N

37	Sushilabai	35	F	Housewife	10425	Dimethoate	Y	Y	Y	1086	Y	N	Y	N
38	Vijaylaxmi	25	F	Housewife	5350	Monocrotophos	Y	Y	Y	965	Y	N	Y	N
39	Savitha	23	F	Housewife	3256	Malathion	Y	Y	Y	189	N	N	Y	Y
40	Muttayya	35	M	Farmer	689	Monocrotophos	Y	Y	Y	1736	Y	N	Y	Y
41	Nirmala	25	F	Housewife	11361	Fornothion	Y	Y	Y	241	N	N	N	N
42	Vinod	23	M	Farmer	11772	Ethion	Y	Y	Y	367	N	Y	N	N
43	Suman	18	F	Housewife	11890	Quinalphos	Y	Y	Y	1456	N	N	N	N
44	Ravi	22	M	Farmer	11897	Dichlorvos	Y	Y	Y	798	Y	N	Y	N
45	Anasubai	21	F	Housewife	11186	Parathion	Y	Y	Y	964	Y	N	N	N
46	Roopali	23	F	Labourer	2699	Chlorfenvinphos	Y	Y	Y	723	N	N	N	N
47	Mallamma	35	F	Labourer	3508	Fornothion	Y	Y	Y	1384	N	N	N	N
48	Maitra	15	F	Student	1927	Monocrotophos	Y	Y	Y	1127	N	N	N	N
49	Parsappa	30	M	Farmer	9573	Quinalphos	Y	Y	Y	1083	N	N	N	N
50	Kasturibai	45	F	Housewife	9843	Ethion	Y	Y	Y	1268	N	N	N	N

	PRIOR TO DISCHARGE						
ARRYTHMIA	SINUS T	SINUS B	ST-T CHANGES	PROLONGED QT	ARRYTHMIA	MORTALITY	VENTILATOR SUPPORT
N	N	N	Y	N	N	N	Y
N	N	N	N	N	N	N	N
N	N	N	Y	N	N	N	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	Y	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	Y
N	N	N	N	N	N	N	Y
N	Y	N	N	N	N	N	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
Y	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
Y	N	N	N	N	N	N	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
Y	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	Y	N	Y	N	Y	Y	Y
N	N	N	Y	N	N	N	N

N	N	N	N	N	N	N	N
N	Y	N	Y	N	N	N	N
N	N	N	Y	Y	N	Y	Y
N	N	N	N	Y	Y	Y	Y
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N