

Dissertation

**A STUDY OF MYOCARDIAL INJURY IN
ORGANOPHOSPHOROUS POISONING**

Submitted to

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CHENNAI – 600032.**

In partial fulfillment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE



**DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001.
APRIL 2015**

CERTIFICATE BY INSTITUTION

This is to certify that **Dr. V.GIRIDHARAN**, Post - Graduate Student (MAY 2012 TO APRIL 2015) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on “**A STUDY OF MYOCARDIAL INJURY IN ORGANOPHOSPHOROUS POISONING**” under my guidance and supervision in partial fulfilment of the regulations laid down by the Tamilnadu Dr.M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2015.

Dr.R.JAYANTHI M. D.,

Professor and HOD

Department of General Medicine

Govt. Stanley Medical College & Hospital

Dr. AL. MEENAKSHI SUNDARAM M.D., D.A.,

Dean

Govt. Stanley Medical College & Hospital

Chennai 600001

CERTIFICATE BY THE GUIDE

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Dr.P.VASANTHI., M.D.,

Professor

Department of General Medicine

Govt.Stanley Medical College

Chennai-600 001

DR.R.S.MURALIDHARAN.,M.D.,

Professor

Department of General Medicine

Govt.Stanley Medical College

Chennai-600 001

DECLARATION

I **Dr. GIRIDHARAN. V** solemnly declare that I carried out this work on “**A STUDY OF MYOCARDIAL INJURY IN ORGANOPHOROUS POISONING**” in the Intensive Medical care Unit of Government Stanley Hospital during the period February 2014 to September 2014. I also declare that, this bonafide work or a part of this was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M.D. Branch I, General Medicine Degree examination

DR. GIRIDHARAN. V

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INTRODUCTION

Organophosphorous (OP) pesticide self-poisoning is estimated to kill around two lakhs population per year, largely in pacific asian region, majority of incidences takes place in rural populations and is mostly due to impulsion. In western population the scenario is different that is more incidence of poisoning with drugs takes place.

In India the mortality is around one fourth to one fifth, but in western it is only less than one percent⁽¹⁾. Even developed countries are prone to military or terrorist attacks with nerve agent OP compounds.

The main mechanism of action of all OPs is that they inhibit the enzyme acetyl cholinesterase. Majority of the mortality is due to cardiorespiratory compromise. But the clinical manifestations vary with type of insecticide and amount of insecticide consumed.

In a clinical study 38 percent of patients require intubation for respiratory compromise following that the death rate was also high⁽²⁾. If cardiac

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• ETHICAL COMMITTEE APPROVAL LETTER	
• MASTER CHART	

LIST OF ABBREVIATIONS

Ach	Acetylcholine
Anti-ChE	Anticholinesterase
AOPP	Acute organophosphorus poisoning
CPK-MB	Creatine Phospho Kinase MB
CT	Concentration time
CYP	Cytochrome P
DDT	Dichlorodiethyltrichloroethane
EPA	Environmental protection agency
HI-6	Asoxime
LuH-6	Obidoxime
IMS	Intermediate syndrome
LD50	Lethal Dose 50%
NCRB	National crime records bureeau
NTE	Neuropathy target esterase
OPC	Organo phosphorus compound
OPIDN	Organophosphate-induced delayed neuropathy
PAM	Pralidoxime
PON1	Paraoxonase 1
POP	Peradeniya organophosphorus scale
PPE	Personal protective equipment
TEPP	Tetraethyl pyrophosphate
TMB-4	Trimedoxime

INTRODUCTION

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In a clinical study 38 percent of patients require intubation for respiratory compromise following that the death rate was also high ⁽²⁾. If cardiac complications are not recognised early it can be fatal.

The exact pathogenesis of cardiac complications has not yet been defined. A few important studies have been carried out both in India and abroad to study the cardiac complications and electrocardiographic changes in organophosphorous poisoning.

The current study was carried out to understand the cardiac manifestations of organophosphorous poisoning with special reference to cardiac enzymes and ECG changes.

REVIEW OF LITERATURE

In organophosphorous intoxicated patients, cardiac manifestations are not uncommon. In most patients the ECG may show, simple effects to lethal changes. These includes sinus tachycardia, repolarisation abnormalities including ST segment deviation and T wave abnormalities ,Q-T prolongation, arrhythmias and A-V blocks⁽³⁾.

The mechanisms of cardiotoxicity are not clearly understood. Apart from direct toxic effects of the OP compounds, dyselectrolemia, and acidosis are mainly due to increased sympathetic and/or parasympathetic activity are the reasons behind myocardial damage in organophosphorous intoxication. The reported prevalence of various electrocardiographical changes in OP compound is 89.1 % ⁽³⁾.

Myocardial damage is caused by both sympathetic and parasympathetic over activity ⁽⁴⁾. Yasue et al in 1974⁽⁵⁾ discovered that parasympathetic over activity leads to coronary artery spasm; following that Horio et al ⁽⁶⁾ injected acetylcholine into intracoronary vessels and demonstrated coronary vasoconstriction.

Kiss and Fazekas identified transient myocardial infarction in five patients among the 168 cases included in a study ⁽⁷⁾. Diffuse myocardial damage was found at autopsy in two cases of Malathion intoxication ⁽⁸⁾.

Kathi et al conducted a study in 37 patients ⁽³⁾ for a 3 year period of cardiac complication following organophosphorous intoxication; out of 37, 62.5% that is 23 of 37 patients had cardiovascular injury, of which 29.7% that is 11 out of 37 developed electrocardiographic changes suggestive of injury to myocardium (ST-T Changes); three out of 37 died, that is 8.1% (3/37).

CP Dalvi et al ⁽⁷⁾ studied the correlation of electrocardiographic changes in organophosphorous poisoning with its prognosis. Abnormal ST-T changes and progressive fall in voltage and or low voltage were the commonest ECG changes encountered. These occurred significantly more often in patients with moderate or severe poisoning ($p < 0.001$). The 17 patients (5 moderate, 12 severe) with a combination of these ECG abnormalities required higher doses of atropine (mean 30 mg) and, in the 12 who survived, the ECG took longer (mean 5.5 days) to normalize (despite normal clinical recovery rate) as compared to other cases. All fatal cases in the study had both these ECG changes.

WANG Jian-dong et al ⁽⁹⁾ studied the dynamic changes of cardiac enzymes and the acute poisoning with organophosphorous in Department of Emergency, Sichuan Provincial People's Hospital. Fasting serum level of troponin T and cardiac enzymes (CK-MB, CK, AST, and LDH) in 92 patients with acute organophosphorous poisoning (AOPP) were measured after poisoning 1,2,3,5 and 7 days, and were measured one time in normal control group as well. There was an increase of different levels in troponin T and

cardiac enzymes along with the degree of (AOPP). They concluded that the level of cardiac troponin T and cardiac enzymes in patients with AOPP may be as useful markers of degree of poisoning and prognosis.

GUO Ya-ying et al conducted a study at the People's Hospital of Yingshang, Anhui. They studied the applied value of serum cardiac troponin T(cTnT) for diagnosing myocardial lesion in the acute organic phosphorous pesticide poisoning(AOPP). The serum cTnT and CK-MB were significantly higher than that in control group and increased with the degree of poisoning. They concluded that the level of serum cTnT increase significantly with the serious degree of AOPP and was sensitive marker of myocardial injury.

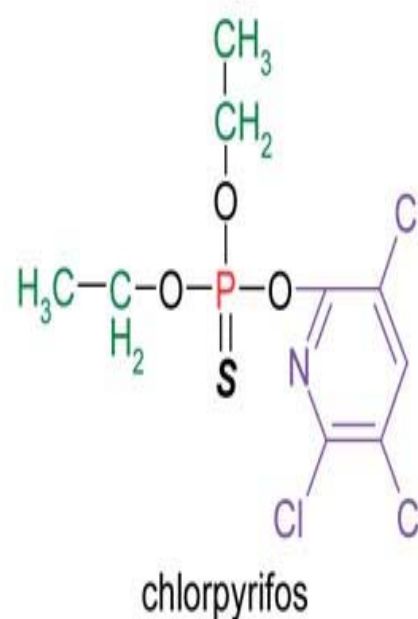
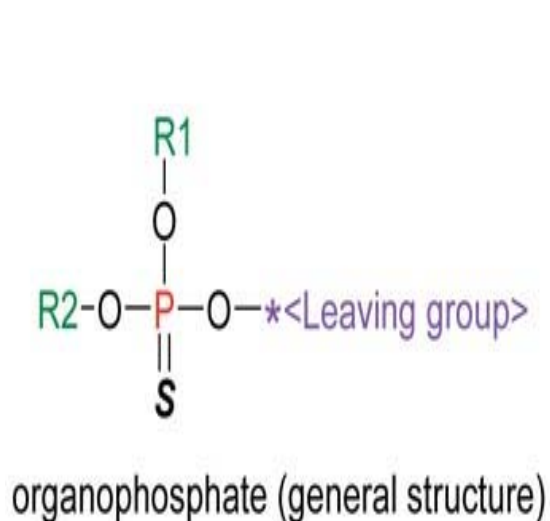
HISTORY OF ORGANOPHOSPHORUS COMPOUNDS

Two men first involved in research of OPC compounds were Jean Louis Lssaigne and Philippe de Clermont (1854). cholinergic effects of OPC was first described by German chemist Willy Lange and his graduate student, Gerdevon Krueger(1932).

In World War II Germans used the first OP compound tetraethyl pyrophosphate because of scarcity of nicotine. Nicotine is a botanic insecticide used in wars. In 1854 tetraethyl pyrophosphate was first produced. Then Germans discovered the OP nerve agents “soman, sarin, tabun” and used them in World War II. They discovered it’s lethal to humans.

Wide production of OP compounds occurred after World War II by Americans with the help of Schrader, s lab. Parathion came into market first and then Malathion followed by Azinphosmethyl. In 1970 Heptachlor, DDT, Dieldrin are banned. Subsequently these organophosphorous compounds became popular. The mechanism of action of OP compounds was discovered after mass intoxication and suicidal attempts like Jamaican ginger palsy (1930). Tokyo subway incident which was happened in 1995 was due to a religious sector (Aum Shinrikyo) used sarin to intoxicate people. In India also at Margrawa in 2005 at a social event due to accidental ingestion of ethion contaminated food, 15 people were intoxicated.

STRUCTURE OF ORGANOPHOSPHATES



Organophosphates are complexly structured compounds with few same chemical features. The structure of organophosphates includes a phosphorus molecule with a double bond to sulfur (P=S) or oxygen (P=O) and two organic side chains (R1 and R2), and with a leaving group (additional side chain- X).

The group which leaves is peculiar to the individual OP and may be cyanide, thiocyanate, phosphate, halide, thiophenoxy, and carbamate or phenoxy group. The R1, R2 groups may be alkyl / aryl groups and, in most of the common OP compounds, are either two ethyl or two methyl ester groups which forms the diethyl (diethoxy) /dimethyl (dimethoxy) OP compounds.

Chemical Classification of Representative Organophosphorous Compounds

Group A, X = halogen, cyanide, or thiocyanate leaving group;

group B, X = alkylthio, arylthio, alkoxy, or aryloxy leaving group;

group C, thionophosphorus or thio-thionophosphorus compounds;

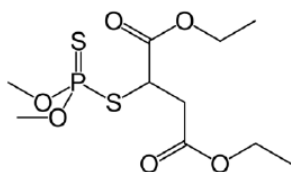
group D, pyrophosphates and similar compounds;

group E, quaternary ammonium leaving group.

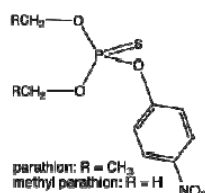
R1 can be an alkyl (phosphonates), alkoxy (phosphorates) or an alkylamino (phosphoramidates) group.

Figure: I Chemical structures of some OP compounds.

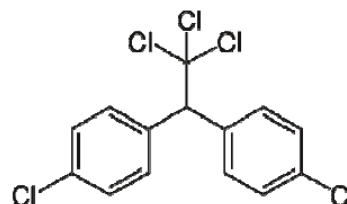
Malathion



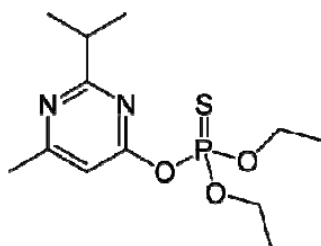
Parathion



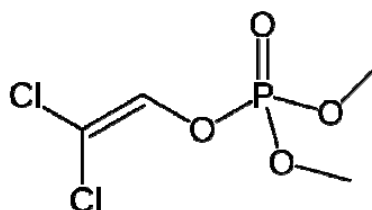
DDT



Diazinon



Dichlorvos



EPIDEMIOLOGY

a)Global Status:

More than three fourth of pesticide related hospital admissions are due to organophosphate compounds and are associated with lethal human effects ⁽¹⁰⁾.

Use of organophosphate insecticides increases as compared to organochlorides like DDT because of their unstable nature which ends in rapid hydrolysis and reduced accumulation in environment, because of the easy availability leads to higher incidence of human toxicities.

In US the environmental protection agency estimated that more than three thousand admissions were occurred due to insecticide poisoning, and the mortality rate was 10 percent in adults and 50 percent in children in 1970s⁽¹¹⁾

American Association of Poison Control Centres in 1983 estimated that total no of poisoning with insecticides were around 77,000, of which 33,000 were due to OP compounds.

In 1990 WHO published ⁽¹²⁾ from the available data that thirty lakhs intoxications due to pesticides took place, out of that 2 lakhs twenty thousand people died. This was the first publication by WHO. Subsequently in 2001 WHO published that eight lakhs forty nine thousand people die due to pesticide poisoning yearly⁽¹³⁾.

So the trend shows increasing incidence of suicidal tendency globally, out of this majority occurred in Asian countries with in rural population that is more than 60 percentage of mortality ⁽¹⁴⁾. In suicidal methods incidence of pesticide poisoning is higher than hanging and any other forms of suicidal nature.

Bangladesh national data recently estimated around 14 percent of mortality in females with the age range from 10 to 50 were the result of self harm mainly because of pesticide intoxications ⁽¹⁵⁾ .

In Sri Lankan Island at the period of 1995 most common cause leading to nursing home mortality was due to poisoning with pesticides especially in people who were pertaining to rural population ⁽¹⁶⁾ .

Globally especially in Asian countries, due to easy availability of pesticides because majority of people depends on agriculture for survival, cause of self harm is mainly due to these agents. This predisposes the health care staffs at risk of exposure to these agents, which can cause health risk.

b)national status

One fourth of nation's GDP is from agriculture, so it's one of the major contributions to economy. In India we are widely using pesticides. In Indian pesticide industry there are around 40 large companies and 400 formulators.

These highly hazardous products are available with ease to Indian people because of the marketing system is fragmented and also there is minimal

awareness among people regarding the adverse health outcomes. But outside India the global statistics is different, 60% of the marketing is done by five top multinational branded companies.

c) Toxic exposure to pesticides can occur at many levels

1) Before spraying— because of easy access for children, lack of adequate labelling

2) During mixing

3) During spraying and

4) After spraying operations, Spray operators and bystanders can be affected. Low cost and easy availability of highly hazardous pesticides at hand increased the incidence of intentional pesticide poisonings⁽¹⁷⁾ .

Number of cases of pesticide poisoning occurring in India per year has been estimated by G. Ravi et al (2007) is around 76 000, and it is higher numbers than NCRB. In the same year Gunell et al, calculate that the number of intentional cases as 1.26 million per year⁽¹⁸⁾ .

PATHOPHYSIOLOGY OF TOXICITY

OPC COMPOUNDS WITH MODERATE AND HIGH TOXICITY

HIGHLY TOXIC	MODERATELY TOXIC
Phosphamidon (dimecron)	Fenthion (baytex, entex)
Ethyl parathion (folidol-lipid soluble)	Malathion (finit)
Chlorothiophos (celathion)	Fenitrothion (tik-20)
Carbophenothion (trithion-lipid soluble)	Diazenon (spectacide)
Methyl parathion (moon bug liquid)	Temephos (abate)

Inhibition of acetyl cholinesterase by OPC

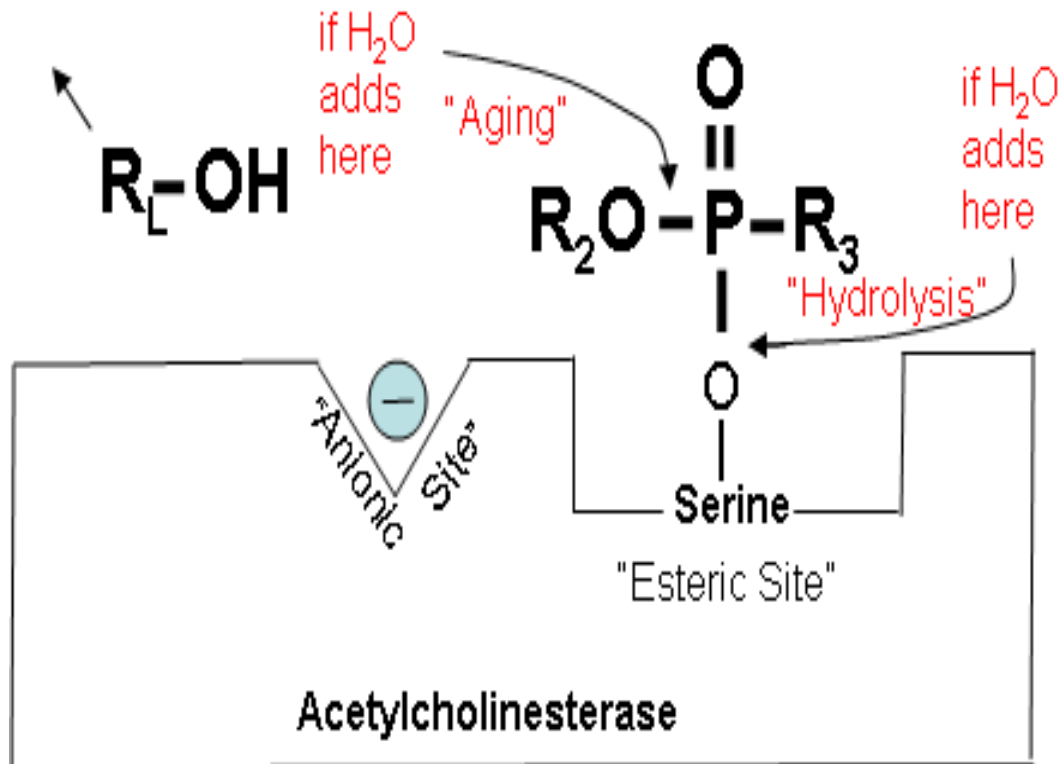
Organophosphates bind and inhibit acetyl cholinesterase enzyme thereby producing toxic effects. It binds at the active serine site. Due to inhibition of enzyme acetylcholine accumulates at peripheral and central muscarinic and nicotinic receptors. Accumulated acetylcholine at nerve terminals, initially stimulates, and then paralyzes neurotransmission. Acetyl cholinesterase physiologically breaks acetylcholine by hydrolysis into two inactive substances that are choline and acetic acid. Because catabolism of acetylcholine, its availability at synaptic junctions is reduced, and also choline is available for reuptake and reproduction of acetylcholine.

Due to inhibition of acetyl cholinesterase number of acetylcholine molecule is high at neuromuscular junction which leads to excitatory effect on post synaptic junction. When acetyl cholinesterase is inhibited, acetylcholine

cannot be broken down and accumulates at the nerve or myoneural terminal, leading initial postsynaptic excitation followed by inhibition at neuromuscular junction. Because of depolarizing blockade at postsynaptic junction inhibition happens. But RBC membrane also exhibits cholinesterase activity and it's called as RBC cholinesterase.

In serum and liver there is butyryl or pseudo cholinesterase which plays major role in xenobiotic metabolism. Since RBC acetyl cholinesterase activity resembles closely with neuronal acetyl cholinesterase it can be taken to measure the physiological activity of cholinesterase enzyme ⁽¹⁹⁾. But measuring butyrylcholinesterase is a simple technique; this is most widely performed in health care facilities.

STRUCTURE OF ACETYL CHOLINESTERASE AND MECHANISM



- It has a pit with a catalytic region and serine binding region
- 1) organophosphorous axon which is electrophilic binds (reversible) to the serine active region forming a complex (Michaelis-Menten)
 - 2) After that rapid phosphorylation of the serine residue happens.
 - 3) Then release of leaving group of organophosphorous happens (X)
 - 4) Now the organophosphorous is covalently bound to the enzyme pit.
 - 5) After this conformational change in the enzyme occurs.
 - 6) After the conformational change acetylcholine cannot bind to the active region of the enzyme.

7) So catalysis of acetylcholine is inhibited ⁽²⁰⁾ .

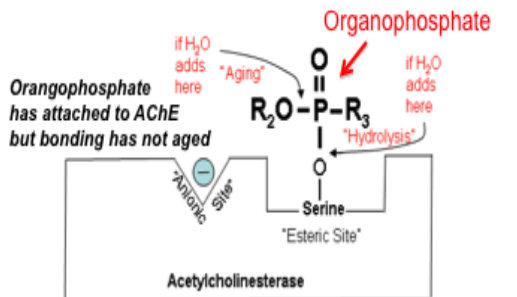
Aging and reactivation of acetyl cholinesterase

After these reactions the phosphorylated enzyme will undergo into two different reactions

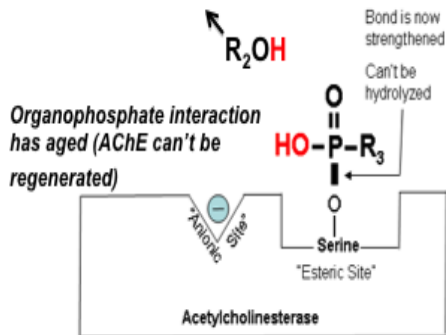
- a) The enzyme can be irreversibly bound or aged
- b) Inactivated by dealkylation which leads to cleavage of one of the R groups, because of which the substituted phosphoric acid residue is firmly attached to the enzyme site.

Aging and reactivation

Organophosphate Aging – chemical stabilization of phosphate bond to AChE occurs over time

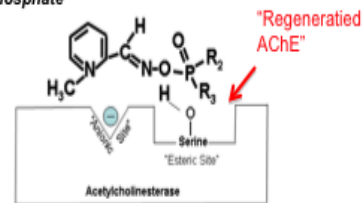
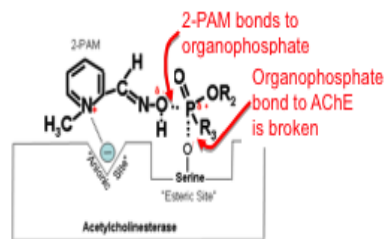
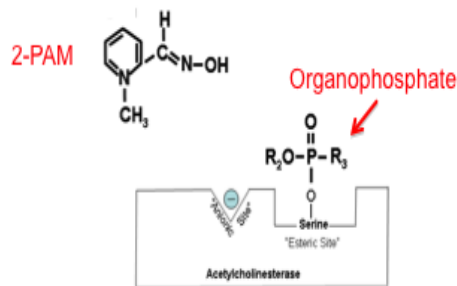


The rate of aging is unique for each organophosphate compound, and can occur over minutes to days depending on the agent



The departure of the R₂ alkyl group (aging) results in increased electron sharing between the phosphate group of the organophosphate & the serine on AChE. This bond can't be broken by 2-PAM.

Pralidoxime (2-PAM) prevents aging & regenerates AChE



Modified from: CDC Case Studies in Environmental Medicine
<http://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=23>

Depends on the specific organophosphorous the aging process varies.

Reactivation of acetyl cholinesterase

Alternately enzyme reactivation can happen when serine organophosphorous bond is hydrolyzed. Reactivation of enzyme happens faster when nucleophilic oxime is added. Or reactivation may be dead slow for organophosphates which contains di-ethyl group.

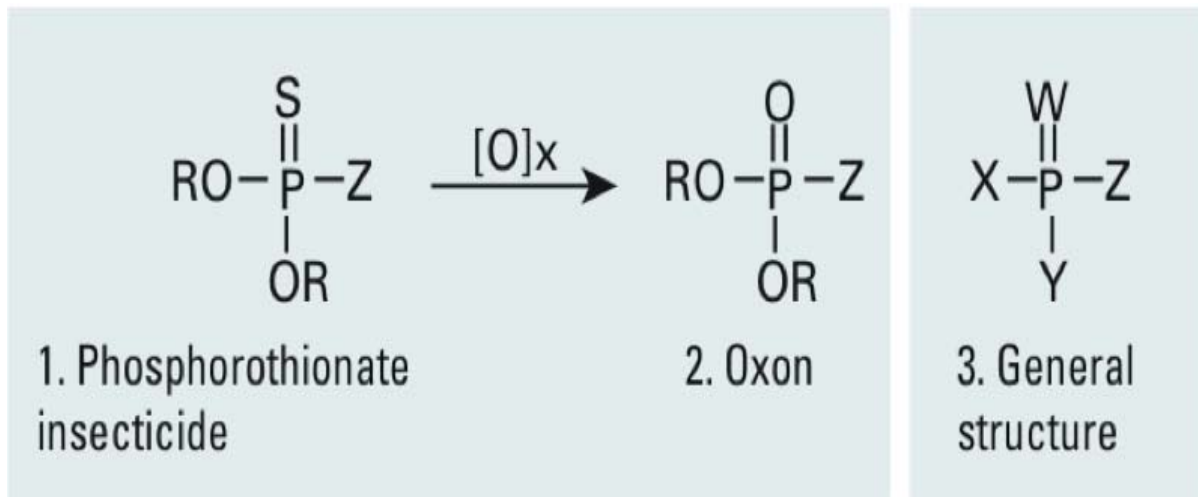
Depending upon which R group is attached the rate of reactivation process or aging process depends. When the R chain is smaller the reactivation is fast, when the R chain is branched due to steric hindrance it increases the bond stability so reactivation is delayed.

To support this dimethyl organophorous compounds which are phosphorylated will undergo rapid reactivation than di-ethyl OP compounds, dimethyl OPs have significantly faster rates of spontaneous reactivation and aging (half lives of about 0.7 hours and about 3.7 hours, respectively) than diethyl OPs (half-lives of 31 hours and 33 hours, respectively).

In spite aging is rapid for di-methyl OP compounds, they are more resistant to oximes especially pralidoxime. The need of oximes to reactivate Di-ethyl organophosphorous compounds are more⁽²¹⁾.

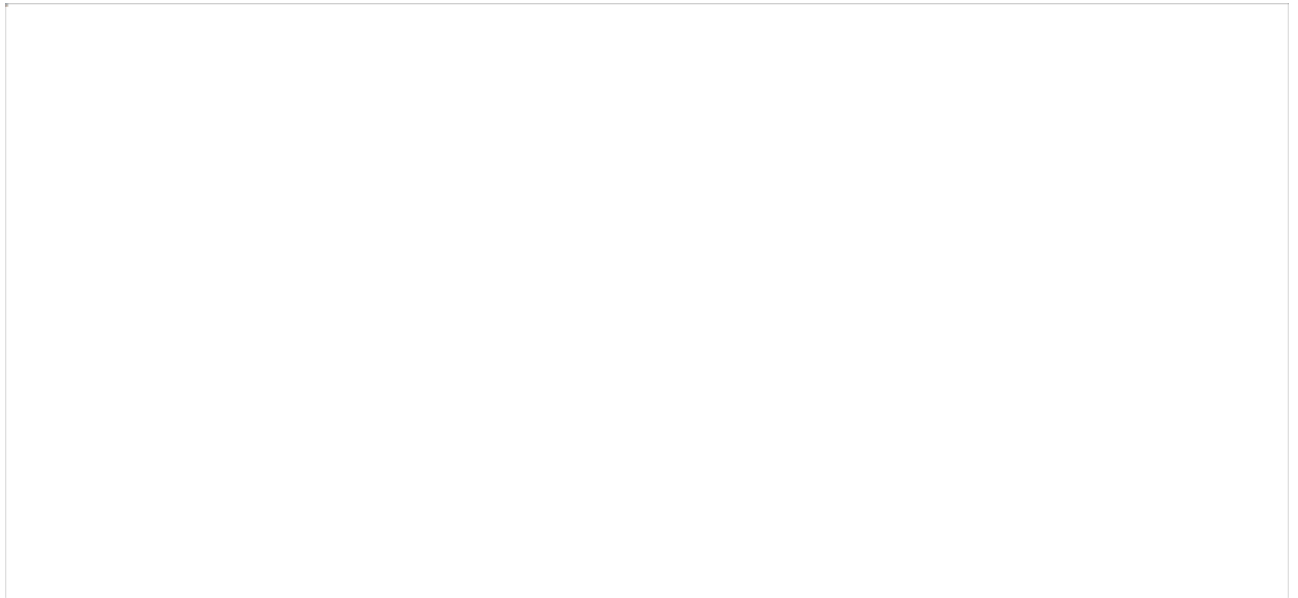
In spite of all these things, the enzyme will not be a candidate for reactivation either by endogenous hydrolysis or oxime treatment when it is aged. The inhibition of acetylcholinesterase does not depend on equilibrium reaction and is mostly depends on the concentration of organophosphorous present at the enzyme level.

What happens when a person is exposed to OPC?



The organophosphates starts forming oxons, at one time there is a nadir in oxon concentration, then it diminishes; there is also a decline in organophosphorous concentration. In spite of decreasing serum levels of oxons and OP compounds the inhibiting action will be continued because of covalent

bonding.

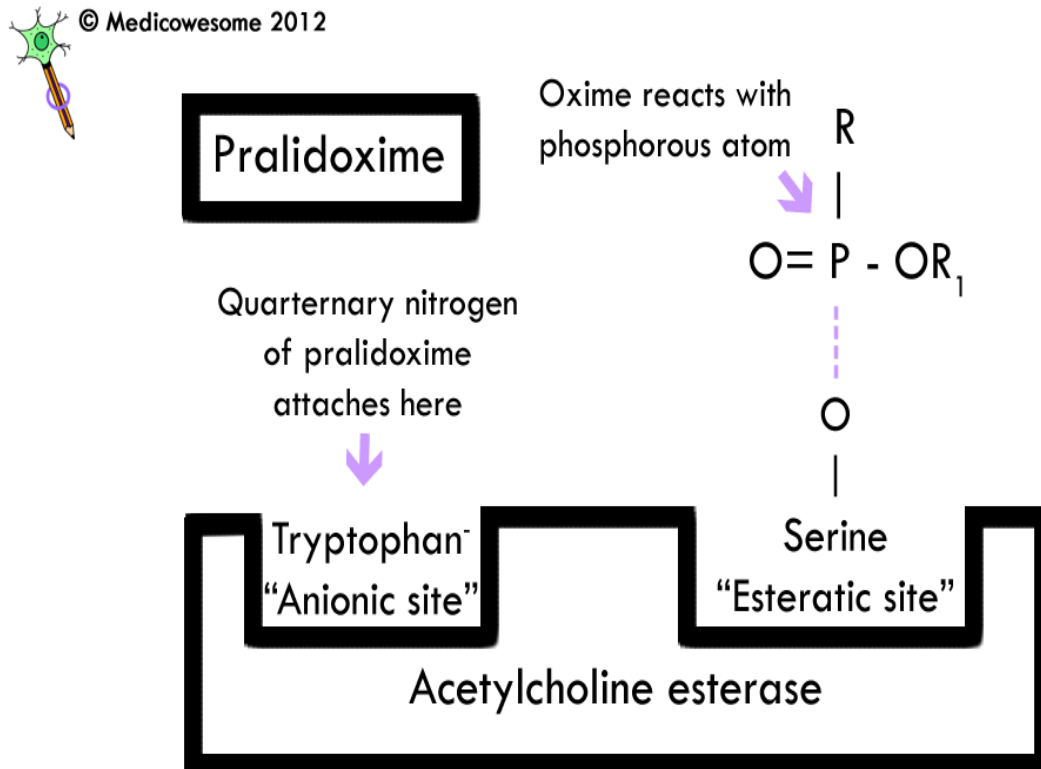


Physiologically, people who are exposed low level of functioning enzyme is left without binding.

Once this upper limit is reached, removal of circulating OP not even enhances the functionality of acetylcholinesterase. Then the catalysis of acetylcholinesterase is only based on restoration of uninhibited enzyme.

Recovery may be fast with few di-methoxy organophosphorous compounds due to reactivation by endogenous route, in these cases rapid decontamination can speed the patient's recovery, but dimethoatethe is an exception.

Reactivation by oximes



The tendency of oximes to reactivate the enzyme is based on several factors

- 1) Organophosphorous structure
- 2) Duration of oxime at the active region
- 3) Concentration of the oxime.
- 4) Transient complex is formed during the reactivation process (oximes with activated acetylcholinesterase)

- 5) This transient complex follows saturation kinetics
- 6) So reactivation of acetylcholinesterase does not occur after saturation.
- 7) Oxime while interacting with OPC, it removes the organophosphorous from the enzymatic site, meanwhile it forms an oxime complex which is phosphorylated.
- 8) This phosphorylated complex strongly inhibits the enzyme acetylcholinesterase.
- 9) In addition to this oximes itself has the ability to inhibit acetylcholinesterase.
- 10) The overall result is even with pralidoxime or other oxime therapy there will be unrecognized mild elevation of blocked acetylcholinesterase enzyme and there may be a clinical worsening ⁽²¹⁾ .
- 11) Phosphorylated oxime complex formed with PAM will disappear quickly since because of unstable nature, and there will not be any clinical impacts. So there is no significant variation.
- 12) If the oximes combines with acetylcholinesterase and forms phosphorylated oximes, and emits the OPC, due to the stoichiometric property its reaction takes place with one molecule of enzyme only (personal communication, Peter Eyer, 2006).

13) Stable phosphorylated oxime is produced by Obidoxime,so, so it can have clinical impacts, but this is yet to be studied in humans ⁽²²⁾ .

Delayed toxicity

Fenthion like OPC has some properties which can lead to prolonged and delayed toxicity in humans, inspite of oxime treatment. The mechanisms behind this are

- a) High lipid solubility
- b) Prolonged elimination
- c) Requirement of bioactivation
- d) If exposure amount is high.
- e) As the organophosphorous is released from fatty tissues continuously, the newly regenerated acetylcholinesterase is again inhibited.

PROPERTIES OF ANTI-CHOLINESTERASE

Pharmacological properties of anti-ChE agents are predicted by

- a) Identifying the sites where acetylcholine is released by nerve stimulation,
- b) Amount of nerve impulse activity
- c) Acetylcholine response in the tissues which effects.

The anti-cholinesterase can lead to the bellow mentioned outcomes:

- (1) Muscarinic stimulation of autonomic structures.
- (2) Initial excitation and following inhibition of skeletal muscle and autonomic ganglions due to action on nicotinic receptor and
- (3) Cholinergic receptor excitation followed by occasional inhibition of central nervous system.

Almost all the above mentioned effects will be seen after lethal dose of anti-ChE agents. But when the doses are small, particularly those used therapeutically, several modifying factors are significant.

Generally quaternary ammonium compound does not enter into cells through cell membrane easily.

So these are not absorbed by the gut / dermis and the BBB prevents it to enter into CNS after moderate doses. On the other hand, such compounds act preferentially at the neuromuscular junctions of skeletal muscle, exerting their action both as anti-ChE agents and as direct agonists.

They have comparatively less effect at autonomic effector sites and ganglia.

The opposite happens with fat soluble anti-cholinesterase, they are readily absorbed following oral ingestion and at the same time it has its action at central as well as peripheral regions, and they may dissolve in fatty tissues for prolonged duration. Lipid-soluble organophosphorous agents also are well

adsorbed through the epidermis, and the agents with evaporating nature are easily transferred readily across the alveoli of lung.

MYOCARDIAL INJURY IN OPC

The mechanism of which OPC induced myocardial damage accordance with Ludomirsky et al has got 3 levels

1) Short duration of raised sympathetic activity presenting with period of intense increase in sympathetic tone manifested by sinus tachycardia;

(2) second phase that is extended parasympathetic tone featured by ST segment -T wave changes, trio ventricular blocks of any degree ,altered rhythm

pattern and even VF in electrocardiography and also associated with hypoxemia .

(3) Third level with the following ECG changes that is prolonged QT , pleomorphic tachycardia and clinically as cardiac arrest are specific.

Appearance of 3rd level changes can happen either as early following poisoning or at times takes many days following intoxication even after disappearance of signs and symptoms of intoxication.

Several factors are there behind arrhythmias in later parts of intoxication. In fact there is a composite histopathological and physiological influence with clinical and laboratory features.

It is obvious that OPC can cause direct cardiac injury.

Marosi et al, postulated that the electrophysiological and pathological alterations are associated with intensity of poisoning, not with reduced activity of enzyme or atropine. In animal studies it is documented that following OPC exposure electrocardiographic changes happens first followed by reduction in cholinesterase activity and these changes are dose related. So it is concluded that QT prolongation in OPC is due to direct toxicity to myocardium, and it is unrelated to cholinergic stimulation.

Some literature shows that due to sustained action of Ach at vagal nerve endings, pathological damage to cardiac muscle happens

The heart musculature is innervated by autonomic nervous system through sympathetic as well as sympatholytic nerves. Acute OPC intoxication deforms the function of ANS, causing in coordination which in turn leads to cardiotoxicity

There are studies that suggest that the morphologic damage can be caused by continuous vagus nerve stimulation (due to the liberated acetylcholine).

Man-mug et al postulated altered T waves and extra systolic pattern in electrocardiography in described in dogs with stimulation of vagal nerve.

Post-mortems studies in animals resulted in cardiac infarcts in papillary muscle and other areas & also dark, mottled cardiac tissue.

The severity of cardiac injury corresponds with the stimulated time by Ach through vagus. Atropine treated animals lived two folds higher than untreated ones; the atropine given animals also exhibited no cardiac injury.

Hall et al study postulated that cardiac injury is through Ach, which in turn caused by vagal stimulation. The above mentioned previous study goes hand in hand, with Hall et al study.

Brief administration of NA in rabbits, cats & dogs 3) leads to catecholamine release which leads to cardiac injury. This confirms that initial sympathetic over activity in OPC poisoning which cause cardiac compromise. Studies show that this injury can be avoided by administering sympathetic blockers.

Parasympathetic stimulation is also plays a role in disease pathology this is similar to mechanism suggested by Gebbers et al' for myopathy.

It is postulated that acetylcholine injection into coronary vasculature of acetylcholine causes vasoconstriction in a greater number of people with healthy & atherosclerotic coronary vessels. So in addition to hypoxemia as previously coated, with generation of oxygen free radicals (which can cause necrosis of myocardium) & imbalance in perfusion to coronary vessels is caused by hypoxemia and sympathetic stimulation, are the possible causes for myocardial injury in OPC poisoning (in the long run it may lead to cardiomyopathy & further sequelae) cause for high incidence of ST-T changes in ECG in acute stage is also explained by the above mechanism.

But we are not able to substantiate that why these ST-T changes are lasts longer than symptoms subsides. Though its an event associated with compromised perfusion, which is an acute event, we are not able to explain why the ST-T changes persists, unless we conclude it as a chronic cardiac pathology.

Electro chemical mechanism of cardiac injury

The basic pathology is Ach binds with its receptors it releases calcium ions. In OPC poisoning due to excessive availability of Ach, which binds to its receptors, induces a mass inflow of calcium ions into cytosol, which leads to abundant depolarization of, the muscle end-plates, leads to muscular damage.

Salpeter et al⁸ studied the effect of acetylcholinesterase with regarding to muscle. He postulated that acetylcholinesterase by inhibiting the action of Ach in skeletal muscles it diminishes the stimulation rate ,thereby protecting the myocyte from diminishing energy at early stages to delaying myopathy in long run.

From the point of view that, cardiac arrhythmias which are delayed in onset are treated with IV Mg –sulfate. It strongly favours that distortion of calcium ion balance at cellular level has a major role in the pathology of cardiomyopathy in OPC poisoning.

Torsades de pointes

The exact pathophysiology is not clearly known. But during later part of OPC poisoning, main pathology involved is a combination of degenerative and regenerative, so it is concluded that there is focal/ multifocal areas of cardiac muscle injury interspersed with normally functioning cardiac tissue, this can be the reason which potentially leads to re-entry & heterogenous areas of depolarization & repolarization, and that this may result in arrhythmia.

In whom delayed cardiac complication develops?

There is no specific time delay between intoxication and development of cardiomyopathy, it is practically not predictable. It is predicted in few OPCs, especially with nerve gas agent soman, which was used as warfare agent. In soman poisoning reactivation of enzyme takes place for a prolonged duration & because of rapid aging reactivation of the enzyme is limited.

But generally it seems that when the severity of intoxication is more the patients are more prone for delayed cardiac complications like arrhythmias and the causes are complicated and many as mentioned above.

Uncommon and unpredicted late cardiotoxicity can happen even after days or weeks, probable mechanisms postulated are

- (a) Direct cardiac injury due to poison itself
- (b) Hypoxemia & acidosis & dyselectrolytes;
- (c) Reperfusion recovery and healing of injured cardiac tissue
- (d) Autonomic pathology & insufficiency.

Roth et al described that after OPC intoxication there is abundance in FFA which can lead to arrhythmogenic potential. At last, cholinergic stimulus

which induces sympathetic activity at postganglionic fibres, compensatory reflexes, and has toxic adrenergic drive to the myocardium.

CREATINE PHOSPHOKINASE MB

CREATINE KINASE —There are two isoforms of creatinine kinase ,made by M and B chain dimers .

Three combinations are present MM, MB, and BB. They are present in cytoplasm. It contributes to the release of high-energy phosphates into and out of mitochondria.

Distribution of CK

Various tissues exhibit CK isoenzyme activity. But fraction of CK-MB present in cardiac tissue is greater than other tissues. But B chain is also present

in skeletal muscle, in some tissues the percentage goes by 10 percent, radioimmunoassay technique detects them easily. Skeletal muscles have more CK/gm than myocardium.

Because of high fraction of CPK in skeletal muscles, injury to this tissue leads to increase in MB fraction. Added to this during regeneration of tissues after injury results in abundant production of CK and B chain. This is supported by marked elevation CK-MB after a long run / excessive muscle strain.

Metabolism

Major part of CK is catabolised by local mechanism / lymphatic's. Hence above local mechanism increases local blood flow hence increase in exit of CK into plasma.

Total CK measurements for the detection of cardiac damage

Because of wider distribution of CK, it is not specific for myocardial injury, the specificity increases with CK-MB. To consider increase in CK it should increase at least 2 times. But in elderly people due to reduction in muscle mass, normally it may be within lower range. In MI in these people total CK will be in normal range but there will be an elevation in CK-MB. Because of these total CK is not useful to detect cardiac injury.

CK-MB fraction for diagnosis

CK-MB assay can be rapidly performed & simple one. Mass CK-MB is measured by most assays; these are more sensitive than measures of activity. Inclusion of macrokinases is avoided in mass tests. Macrokinases are CK linked IgG and dimers of mitochondrial CK. But activity tests includes these macrokinases. So there is no confounding factors mass test. Think of macrokinases when CK-MB is in higher range (more than 20 %) of total CK.

Specificity and sensitivity

CK-MB is highly specific for myocardial tissue. It was considered as specific marker of myocardial injury for years. After 6 hrs of cardiac injury it starts rising but not in all patients until around 12 hours.

Increase in CK-MB is specific to cardiac damage, with ischemic symptoms when no damage to skeletal muscle. It returns to baseline within 36 to 48 hrs, in contrast increase in troponin, will persist up to 10 to 14 days.

Skeletal muscle damage can confound the diagnosis of an MI and cardiac damage as CK-MB can be released, in the following situations.

- Myocardial injury after cardiopulmonary resuscitation
- Cardio version
- Defibrillation

- Cardiac and no cardiac surgical procedures
- Blunt chest trauma with possible cardiac contusion
- Cocaine abuse

CK-MB has lower fraction with total CK in skeletal muscle than cardiac muscle. So percentage criteria (from 2.5 to 5 percent) is used to differentiate skeletal muscle injury from myocardial injury, it increases specificity, but at the cost of sensitivity in patients with both skeletal & cardiac injury.

In people with chronic skeletal muscle diseases mostly have falsely positive CK-MB when percentage criteria are implemented. The proportion of CK which is CK-MB can be nearly 50 percent with chronic skeletal muscle injury, like dermatomyositis or polymyositis, because of higher synthesis of B chain CK.

Percentage criteria will mislead in the following situations

- Hypothyroidism.
- Renal failure.
- Mixed skeletal & cardiac damage.

Persistent rise in CK-MB occur in carcinogenic shock..But in myocarditis CK-MB levels don't rise mostly except in severe myocarditis.

Elevated CK-MB with normal total CK and CK-MB/total CK ratio

In myocardial damage there will be a 2 fold rise in total CK with a proportionate elevation in CK-MB. Sometimes, there will be a rise in CK-MB without a rise in CK; this has got a grave prognosis.

CK and coronary reperfusion

The time to peak CK levels and the slope of CK-MB release can be used to assess whether reperfusion happened. In 2004 ACC/AHA realised that sequential measures of CK-MB can be helpful to support the occurrence of reperfusion

PHARMACOKINETICS OF OPC

Organophosphorous anti-ChE agents with increased risks of lethal effects have increased vapour pressures, highly lipid-soluble agent and liquid in nature. Most of the agricultural insecticides are less volatile agent. They are mainly used for dispersal as aerosols or as dusts adsorbed to an inert, minute

particulate matter (e.g., diazinon, malathion) Mostly the chemical compounds are entered into the body through the contact with moisture i.e skin and mucous membranes, by the GIT after taking food products which is fortified with these substance, and by the lungs after inhalation⁽²³⁾.

Following their absorption, most organophosphorous compounds are excreted from the body in the urine. Two enzymes such as Plasma and liver esterases are needed for hydrolysis to the corresponding phosphonic acids and phosphoric acids.

The CYPs are responsible for converting the inactive compound to active compound. Phosphorothioates compound (inactive) containing a phosphorus-sulfur (thiono) bond to phosphorates (active) with a phosphorus-oxygen bond. These enzymes also play a Vital role in the inactivation of certain organophosphorous agents.

The organophosphorous anti-ChE agents are cleaved by two enzymes families such as:

- 1)paraoxonases (A-esterases)
- 2)The carboxylesterases .

These two important enzymes are present in the liver and plasma. it helps to hydrolyses number of OPCs by breaking the PCN bonds, PF, anhydride,phosphoester. The low-molecular-weight enzymes paraoxonases are

used for catalysation process which needs Ca^{2+} , whose natural substrate is unclear. Some of them have high density lipoproteins properties which helps for hydrolysis.

Some enzymes of this family have some protective effect in atherosclerosis by controlling low density lipoprotein oxidation and leads to protective effect in atherosclerosis⁽²⁴⁾ Genetic polymorphisms that govern organophosphate substrate specificity and possible susceptibility to atherosclerosis have been found⁽²⁴⁾.

Wide variations in paraoxonase activity exist among animal species. Young animals are deficient in carboxylesterases and paraoxonases, which may account for age-related toxicities seen in newborn animals and suspected to be a basis for toxicity in human beings. Plasma and hepatic carboxylesterases and plasma butyrylcholinesterase are inhibited irreversibly by organophosphorous compounds⁽²⁵⁾. Their scavenging capacity for organophosphates can afford partial protection against inhibition of AChE in the nervous system.

The carboxylesterases also catalyze hydrolysis of malathion and other organophosphorus compounds that contain carboxyl-ester linkages, rendering them less active or inactive. Since carboxylesterases are inhibited by organophosphates, toxicity from exposure to two organophosphorous insecticides can be synergistic.

Absorption:

Absorption of OP compounds depends on various factors as follows

- 1) Solvents present in OPC such as xylene
- 2) Emulsifying agents present in OPC which increase absorption
- 3) Lipophilicity
- 4) Duration of contact with skin. Complete and rapid absorption of powders takes place when the particles are fine.

Other factors involved in absorption kinetics are

- a) The extent of coverage of body surface.
- b) Permeability of clothing's.
- c) Volatile property(for eg. Malathion is less volatile than dichlorvos) ,
- d) Involved skin parts (absorption of parathion is more via skin over head and neck,axillae,and scrotal skin rather than arms and hands)
- e) Personal hygiene.
- f) Eczema over skin and abrasions increases the absorption . In a literature ,average amount of dermal absorption is around two percent of is predicted value for parathion liquid formulations⁽²⁶⁾.

Storage & distribution

Rapid accumulation of organophosphorous compounds takes place in liver, fatty tissues, salivary glands and kidney after systemic absorption. More lipophilic substances are phosphorothioates (P=S), like bromphos, parathion and diazinon. Less lipophilic are phosphates (P=O), like dichlorvos. So the more fat soluble substances are stored heavily in fat which leads to clinical relapse and prolonged intoxication after apparent recovery. Organophosphorous insecticides usually cross the blood / brain barrier.

Biotransformation

Active cholinesterase inhibitors is (P=O) but one which needs activation before biologically active is phosphorothioates (P=S), they are biologically activated as phosphate analogues called as oxon. So the clinical manifestations of phosphorothioates after OPC poisoning occurs late, since it should be biologically activated to oxon before it acts on receptors.

This **activation to oxon** is by desulfuration & oxidation through

- 1) P450 isoenzymes,
- 2) Mono-oxygenase which has flavin,
- 3) N & S oxidation.

The inhibiting oxons are deactivated by hydrolases

- a) Carboxylases &

b) A-esterases (paraoxonase).

Enzymes such as paraoxonase 1 (PON1) contribute to endogenous hydrolysis of organophosphates, prodrugs & lipids. All except few organophosphorous pesticides are catabolised rapidly and excreted through kidney. Only few are found in serum after two days following intoxication.⁽²⁷⁾.

Elimination

Excretion commonly occurs through kidney and a few extent in faeces & through lung during expiration. Few organophosphorous compounds like dichlorvos can be excreted within few hours because it is not fat soluble and not stored in fatty tissues. In contrast inhibiting oxon of chlorpyrifos or demeton-S-methyl can be present in fatty tissues as it is stored heavily in fat.

TOXICOLOGY

OP compounds has various chemicals which vary in physical and biochemical and metabolic properties ,because of this nature the toxicity profile also varies specifically with each agent. The lethal effects also depends on exposure route, amount consumed, contact time with the substance & lastly on individual patient status. Estimation of relative human toxicity is especially based upon the measured oral LD50 in rats. The World health organization

revealed the rating of toxicity in 2002 and classified pesticides as extremely hazardous

(Ia) (liquid state: LD50 < 20 mg/kg); high

(Ib) (20–200 mg/kg); moderate

(2) (200–2000 mg/kg); and slightly potent

(3) When it exceeds >2000 mg/kg it is highly hazardous agents are labelled as Poison or Toxic on commercial preparations. The World health organization classification is different from that proposed by EPA, which classifies organophosphorous compounds as high toxicity (rat LD50 < 50 mg/kg), intermediate or moderate toxicity (LD50, 50–1000 mg/kg) and low toxicity (LD 50 > 1000mg/kg)²⁸.

Thus, lethal doses for humans can vary from a few mg for highly toxic agents like TEPP, to 50 g for the low-toxicity agents like malathion. Even one milligram of nerve agent such as soman /sarin is hazardous to people following inhalation.

For volatile /aerosolized/nerve agents, attribution of toxicity is by a concentration time (Ct) variable that is a better measure of inhalational exposure. For nerve gas agents, the lethal Ct 50 varies from 10 to 400 milligram/minute/m³.

CLINICAL MANIFESTATIONS OF ORGANOPHOSPHORUS

POISONING:

Muscaranic features

DUMBELS	SLUDGE
D-DIARRHOEA,DIAPHORESIS	S-SALIVATION
U-URINARY INCONTINENCE	L-LACRIMATION

M-MIOSIS	U-URINARY INCONTINENCE
B-BRONCHORRHOEA BRONCHOSPASM BRADYCARDIA BLURRING OF VISION	D-DIARRHOEA
E-EMESIS	G-GI DISTRESS
L-LACRIMATION	E-EMESIS
S-SALIVATION	

NICOTINIC FEATURES-	CNS MANIFESTATIONS (LESS WITH CARBAMATES)
MUSCLE FASCICULATIONS(STRIATED)	UNCONCIOUSNESS
MUSCLE WEAKNESS	CONFUSION,FATIGUE
PARALYSIS	TOXIC PSYCHOSIS,SEIZURE
HYPERTENSION	RESPIRATORY DEPRESSION
TACHYCARDIA	ATAXIA,DYSARTHRIA
MYDRIASIS (RARE)	EXTRA PYRAMIDAL FEATURES

Acute Intoxication

Clinical features of acute poisoning manifest by muscarinic and nicotinic signs & symptoms but for extremely low lipid soluble agents manifest by signs referable to central nervous system. Within minutes following exposure to vaporizing agents the clinical manifestation occurs.

On the other hand, the symptomatology is delayed after oral or cutaneous absorption. Depends upon the chemical nature of substances the duration of symptoms varies depends on fat solubility, whether it is an active compound or has to be activated to oxon, the stable nature of the organophosphorous-AChE bond, and whether aging of enzyme occurs.

Exposure to vapours & aerosols or after their inhalation, eye & respiratory manifestations happens initially. Ocular manifestations include papillary constriction, decreased visual acuity, ocular ache, congested conjunctiva & ciliary muscle spasm. Some times when the patient presents with hypotension in organophosphorous poisoning pupillary constriction will not there, because of reflex sympathetic activation.

Respiratory manifestations

Upper respiratory tract manifestations include respiratory effects to rhinorrhea and hyperaemia. In lower respiratory tract due to bronchorrhoea and there may be wheeze and chest tightness

Gastrointestinal symptoms

May present early with nausea, anorexia, vomiting, cramps in abdomen & loose stools.

Skin & others

When adsorption happens through skin can lead to local sweating & muscle fasciculation's are the most common early symptoms. Severe poisoning is manifested by excessive salivation, involuntary urination & defecation lacrimation, sweating, erection of penis, bradycardia, and hypotension.

Neuromuscular

Nicotinic actions at skeletal neuromuscular junction manifest with fatigue, involuntary twitching & fasciculation's followed by muscle weakness & muscle palsy. When respiratory muscle palsy happens leads to respiratory failure which may need intubation and mechanical ventilation. Knockout mice lacking AChE can survive under highly supportive conditions and with a special diet, but they exhibit continuous tremors and are stunted in growth⁽²⁹⁾.

Mice that selectively lack AChE in skeletal muscle but have normal or near normal expression in brain & other tissues innervated by the ANS grow normally & reproduce, but have continuous tremors⁽³⁰⁾. These studies show that cholinergic systems can partially adapt to chronically diminish hydrolytic capacity for AChE.

Central nervous system

The broad spectrum of effects of acute AChE inhibition on the CNS includes confusion, ataxia, and slurred speech, loss of reflexes, Cheyne - Stokes respiration, generalized convulsions, coma, and central respiratory paralysis. Actions on the vasomotor and other cardiovascular centers in the medulla oblongata lead to hypotension.

MORTALITY

Mortality following single acute intoxication may range from < 5 minutes to around a day, depends on the dose, agent ,route & other factors.

Leading cause of mortality is respiratory failure often with cardiovascular compromise. Peripheral nicotinic and muscarinic as well as CNS effects all can lead to respiratory compromise; features are bronchoconstriction, laryngospasm, abundant salivary & tracheobronchial and secretions, reduced Voluntary control over intercostal & diaphragmatic muscles, and respiratory depression at CNS. Hypotension and arrhythmias can result of severe toxicity, and due to hypoxemia and mostly are reversed by mechanical ventilation.

INTERMEDIATE SYNDROME

Intermediary syndrome was first documented by Senanayake in 1987. It is characterised by predominant weakness in flexors of neck, proximal muscles & respiratory muscles ,he also called this syndrome as type II paralysis ³¹ Intermediary syndrome can develop 1-3 days following cholinergic crisis ,then it persists for many days up to few weeks ⁽³²⁾. There are opposite views regarding the presence of persistent low levels of Ach(due to insufficient treatment with oxime) at myoneural junction and intermediary syndrome⁽³³⁾ .

Absence of muscarinic stimulation with reduced cholinesterase activity (continuous antagonism by acetylcholinesterase) is the specific feature pertained to this syndrome ,furthermore except supportive care there is no specific treatment options for this syndrome.⁽³⁴⁾

Nerve Conduction Studies performed throughout the intermediary syndrome phase shows have shown sequential decline in in neuromuscular impulses with repeated stimulation at low rates ,gives the constant result of presynaptic & postsynaptic impulse diminution at neuro muscular junction with desensitization ⁽³⁵⁾ There is no specific etiology at this point , Sri Lankan pralidoxime study throws some light to the etiology but not specific to be taken away Few people suggests giving extra amount of oximes will help in recovery ,but studies yet to come to support this.

DELAYED POLYNEUROPATHY (organophosphate-induced delayed neuropathy or polyneuropathy)

Neuropathy target esterase is abundant in schwan cells which lines the axons. Organophosphorous induced neuropathy is occurs when few organophosphorous compounds blocks these enzymes along with acetylcholinesterase.

It is specially associated with phosphates, phosphoramidates, and phosphonates types of OPCs by inhibiting both acetylcholinesterase and neuropathy target esterase (NTE). During aging which causes detriment in myelin sheath a dying back axonopathy .

When aged, causes loss of the myelin which will not respond to treatment with atropine /pralidoxime ⁽³⁶⁾ .This causes demyelination which is symmetrical

and the patient presents history of cramping pain, paresthesias, tingling, pain & distal extremity weakness.

It takes around three to six weeks for the development of these neurological symptoms following the exposure of toxin and it is progressive in nature for several weeks to months⁽³⁷⁾.

The diagnosis of neuropathy can be supported by measuring lymphocyte neuropathy target esterase (NTE) assay. Decrease in of lymphocyte NTE corresponds with the development of OP-induced delayed neuropathy (OPIDN)⁽³⁸⁾.

No target therapy is available for OPIND, it is only supportive treatment. For mild cases resolution of neurological symptoms can happen over the span of 6 months to a year. But for patients who presents with severe OPIND, have chronic persistent neurological deficits⁽³⁹⁾.

CHRONIC NEUROPSYCHIATRIC SEQUELAE

There are few other neurological & neuropsychiatric sequelae may be pertained to organophosphorous poisoning. Immediately they may present with acute encephalopathy. Patients may develop severe encephalopathy. Chronically they can present with fatigue, short-term memory loss, fatigue, confusion, psychosis, depression, extra pyramidal/ Parkinsonism features⁽⁴⁰⁾

DIAGNOSIS

Organophosphorous poisoning diagnosis is supported by specific clinical findings, like miosis is a strong predictor and history of exposure to a known OP compound. Measurement of RBC /serum cholinesterase level supports the diagnosis .

Electrodiagnostic studies are helpful to confirm it .When red blood cell cholinesterase level drops to less than three fourth the symptoms of OPC intoxication will manifest, when the intoxication is severe the levels will be < 10 percent.

But few studies did not support the positive association with symptom severity and patients outcome ⁽⁴¹⁾.

laboratory findings:

Usual lab studies don't give us any clue usually but there are few exceptions. Occasionally there will be hypokalemia and several case studies indicates that non ketotic hyperglycemia and glycosuria can happen.

In Hayes's study leucocytosis, with or without a left shift, was a common observation ⁽⁴²⁾. Due to parasympathetic activation and increased secretions which causes pancreatic injury, there may be increase in serum amylase levels.

Electrocardiography will give us a various aberrations in acute intoxication such as, sinus tachycardia, sinus bradycardia, AV blocks, ST-T changes & Q-T prolongation and rarely various pattern of arrhythmias ⁽⁴³⁾.

Laboratory findings	significance
Neutrophilic leucocytosis	46%
hyperglycemia	23%
proteinuria	19%
glycosuria	14%
hyperamylasemia	14%

EMG	<p>a)Decrement-increment response to high frequency(30-50)RNS</p> <p>b)Decrement response to high rate RNS (30 -50 Hz)</p>
Acidosis	Poor prognosis

Serum /rbc cholinesterase levels:

Laboratory confirmation of poisoning is documented by reduced Serum / RBC acetylcholinesterase levels. Out of these two enzymes serum acetylcholinesterase activity has got high inter-individual variations, so mild poisoning cannot be established without successive decline in cholinesterase levels . RBC acetylcholinesterase is bound to the membrane and is harmonized with haemoglobin in the RBC, so it will not show variations between individuals.

Because RBC acetylcholinesterase is found in membrane of RBC without reactivation of enzyme by oximes ,the levels will be diminished till the

RBC's die and new erythrocytes develops, so that is up to two to three months the levels of RBC acetylcholinesterase activity is diminished⁽⁴⁵⁾.

Regeneration of neuromuscular junction acetylcholinesterase is rapid as compared to RBC acetylcholinesterase. Butyrylcholinesterase comes to baseline in two to four weeks since its an acute-phase reactant. In around 3% of general population there is baseline depression of butyrylcholinesterase activity level due to genetic variations. Other conditions in which butyrylcholinesterase activity is decreased are pregnancy, hypoalbuminemia, drugs, congestive cardiac failure leading to secondary hepatic injury, parenchymal liver disease and metastatic cancers.

	RBC cholinesterase	Plasma cholinesterase
Advantage	Better reflection of synaptic inhibition	Easier to assay, declines faster
site	CNS grey matter, RBC, Motor end plate	CNS white matter, plasma, Liver, Pancreas, Heart
Regeneration	1% of day	(25-30) in first 7 to 10 days
Normalization	35 to 49 days	28 to 42 days

Use	Unsuspected prior exposure with elevated plasma cholinesterase	Acute exposure
False depression	Pernicious anaemia, Haemoglobinopathies, Anti malarial treatment, Oxalate blood tubes	Cirrhosis, Malnutrition,succinylcholine,codeine Morphine,pregnancy Genetic deficiency

Peradeniya organophosphorous poisoning (POP) scale:

Parameters	Criteria	Score
Pupil size	≥2 mm	0
	<2 mm	1
	Pinpoint	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41–60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Note: 0–3, mild poisoning; 4–7, moderate poisoning; 8–11, severe poisoning

The Peradeniya Organophosphorous Poisoning (POP) Scale is a scoring system introduced by N Senanayake, H J de Silva and L Karalliedde in 1993⁽⁴⁶⁾. Usual clinical features of OPC intoxication are chosen as variables and everyone is assessed on a three-points score which varies from 0 to 2 (Table 4). A score of

- 1 to 3 is considered as mild poisoning,
- 4 to 7 as moderate poisoning and
- 8 to 11 as severe poisoning.

MANAGEMENT

Initial management:

Airway management is the mainstay in managing OP- intoxicated patient . Rapid atropinisation and oxygen are the initial mode of treatment when patients clinically presents with crepitations and excessive bronchial or oral secretions ,hypoxia or cyanosis. Eddleston from Srilanka demonstrated in a cohort study that there is no increased cardiotoxicity with early and rapid atropinisation in a cohort study ⁽⁴⁷⁾.

The antidote should be given till pulmonary oedema subsides and oral and bronchial secretions have dried.

If respiratory compromise occurs during rapid atropinization, it should be should be handled by securing the airway with intubation with or without

mechanical ventilation, and frequent suctioning of oral cavity and airway as well.

In (RSI) that is rapid sequence intubation depolarizing blockers such as succinylcholine though not contraindicated should be used with great caution since its metabolism depends on butyrylcholinesterase. So when this enzyme is inhibited it can lead to prolonged paralysis.

GI loss :

Organophosphorous compound intoxication leads to nitric oxide mediated vasodilatation of GI vessels and leads to moderate to severe GI fluid loss.⁵¹ For this isotonic saline should be infused rapidly by IV. For the patient to become euvolemic around 2 L or more fluid is needed. When hemodynamic compromise is there even with atropine and IV fluids one should go with vasopressors . Among the vasopressors , phenylephrine is chosen because it acts directly on α receptors in adrenergic system ,since intoxicated persons have a relatively normal inotropic state and a reduced systemic vascular resistance⁽⁴⁸⁾.

Seizure

Seizure should be controlled rapidly with drugs acting through GABA like lorazepam, midazolam or diazepam. Aggressive benzodiazepine use during seizure will increase overall survival by reducing cardiac and CNS complications. Widely accepted treatment regimen for adults to control seizure activity is 5 to 10 mg of IM midazolam or 10 mg IV diazepam, for paediatric patients dosing is 0.1–0.2 mg/kg of IV diazepam or 0.1–0.3 mg / kg of midazolam IM with dose titration as required.

Decontamination:

Decontamination is the next priority after initial clinical stabilization of patient. In liquid contaminations when the clothing's are soiled patient will have continuing cutaneous adsorption of OPCs. Thus, as quick as possible, one should undress the intoxicated person then skin should be washed thoroughly with water and alkaline-soap solution. Life saving resuscitation and antidote administration should not be delayed because of the above measures. Undressing eliminates around 85% to 90% of a contaminated OP compounds⁽⁴⁹⁾.

During decontamination care giver should self protect himself or herself with adequate personal protecting equipment especially in OP and nerve agent poisonings. At the site initial decontamination should be done by trained

persons who are handling hazardous materials by protection level of A or B. After transfer of patient to hospital setup, hospital staffs should be equipped with minimum of Level C protection with covering shoes, nitrile, butyl or neoprenenitrile gloves & facial splash protection and impermeable gowns.

Gastric lavage following ester OPC poisoning is debatable. Since organophosphorous esters are strongly emetic, intoxicated persons will vomit before seeking health care. For patients presenting within an hour of ingestion we can go with empirical gastric decontamination of an ingested material. But it is not supported by RCTs. Activated charcoal binds to few organophosphorous insecticides, so activated charcoal through oral route is usually recommended in intoxicated patients through orally.

Aspiration risk

Most of the organophosphorous compounds are dissolved in hydrocarbon solvents. These hydrocarbon compounds have a tendency to cause severe chemical pneumonitis when aspiration into airway occurs. So the advantage of nasogastric aspiration should be balanced against the risk of aspiration pneumonitis⁽⁵⁰⁾.

Anticholinergic agents:

Generous use of atropine (for muscarinic symptoms) and oximes to regenerate acetylcholinesterase is the mainstay in treatment of OP poisoning⁽⁵¹⁾.

Atropine inhibits post synaptic binding of acetylcholine(muscaranic receptors), it crosses blood brain barrier since its a tertiary amine and acts also on central muscaranic receptors.

Atropinization

Atropine takes control over muscaranic symptoms like bronchorrhoea and at times bradyarrhythmias and clinical hypotension. The dosing of atropine is not constant.

And the dosing regime followed by Eddleston and colleagues from srilanka recommends rapid and intensifying doses of cholinergic antagonist (atropinisation) ,followed by maintenance atropine infusion is associated with more success in protecting the airway from secretions and controls other muscaranic symptoms ⁽⁵²⁾.

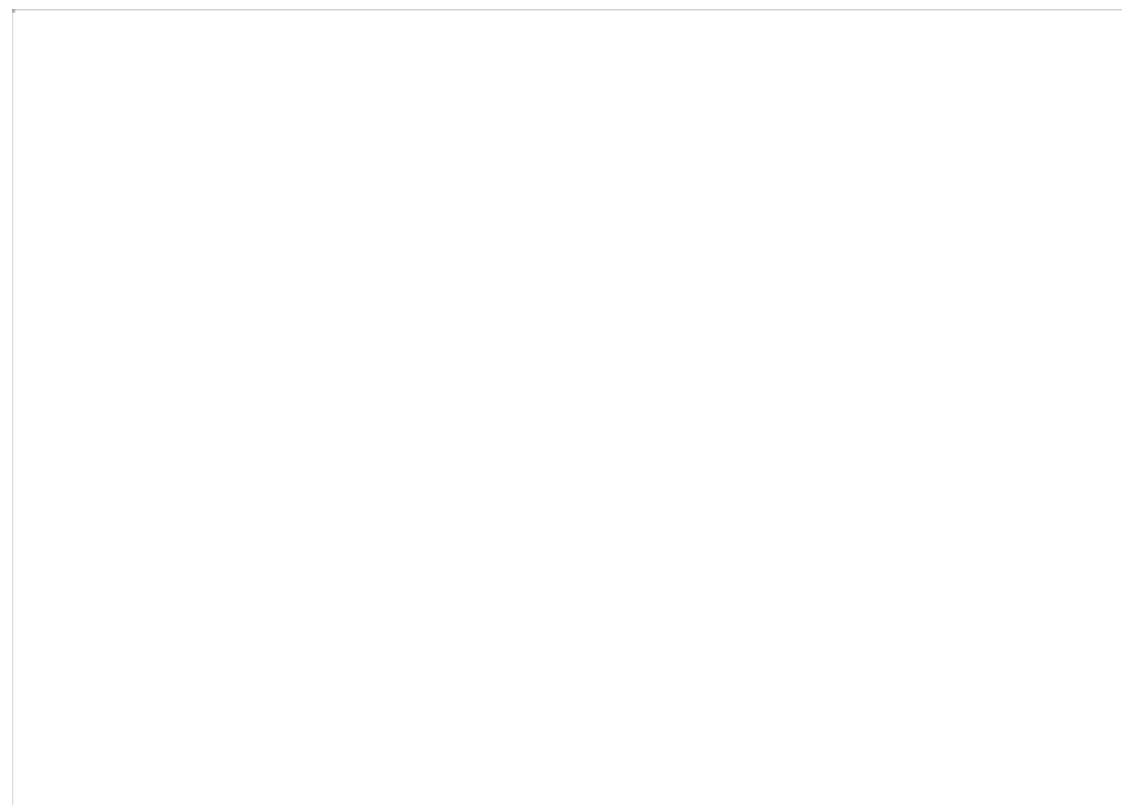
By this regime, patients with muscaranic symptoms are given 1 to 2 mg IV atropine at the beginning, and doubling doses at every five minutes interval

as required. This regime will rapidly give forth a accumulative dose of 25 mg by 20 min and 75 mg by 25 min.

Patients with severe toxicity may need 75 to 100 mg of atropine. Adequate dose of atropinization is assessed by disappearance of secretions from the bronchial tree (clinically- disappearance of crackles)heart rate >80 beats/min, dry skin, and a mean blood pressure > 60 mm Hg or clinical indicators organ reperfusion. Dilatation of Pupil is a late sign of atropinization it lags behind recovery of crepitations and bradycardia (approximately 30 min). But non constricted pupil should be the goal.

Oximes in treatment:





They inhibit OPC and activates the inhibited enzyme . two groups of oximes that are clinically essential are 1) bispyridinium 2)monopyridinium oximes . in treatment pralidoxime which is a monopyridinium oxime is applied widely. Obidoxime (LuH-6, Toxogonin) trimedoxime (TMB-4) and asoxime (HI-6),while the most important bispyridinium oximes and their structure is as below. But still there is no clearcut evidence to use which oxime for clinical effectiveness.

In 1950s Wilson and colleagues discovered PAM-2,soon it was used clinically in parathion intoxicated patients. Among the various oximes described only pralidoxime is used widely. Its structure includes four salts –mesilate, chloride, iodide and metisulfate .

Extensively used one are chloride and iodide salts , but in France , UK and Belgium mesilate & metisulfate are used commonly . Among chloride & iodide, chloride has advantage by having low molecular weight. (Chloride-173,iodide-264)because of low molecular weight it gives more active compounds approximately one to five times than iodide per gram of compound. Also evidence suggests that thyrotoxicity is more when iodide-pralidoxime is used and exposure is prolonged⁽⁵³⁾.

The effectiveness of pralidoxime was studied in Tamilnadu, Vellore in 1990s.the results were inconclusive. It concludes there is harm in infusing low dose pralidoxime. the ineffectiveness could be explained by 1)trial related factors like bias in allocation and suboptimal dose. In spite of its (pralidoxime) benefits with parathion intoxication ,its role has been questioned especially by asian doctors . Of importance, in 1990s two clinical trials in Tamilnadu ,concluded that pralidoxime in low dose infusion can be dangerous.

Absence of advantage may be due to

- 1) Trial design (insufficient dose, or allocation bias)

2) Toxin related that is due to

a) various types of poisons and

b) varied amount of consumption

c) high serum level of toxin which re-inhibits acetylcholinesterase that are reactivated by oximes or

3) patient related factors like

a) delay in seeking treatment

b) if hypoxic brain injury or aspiration pneumonia like complications develop the effectiveness of oximes will be less ,they are common with fast acting pesticides like dichlorvos and parathion. The conclusion of observational studies with pralidoxime and obidoxime to reverse inhibition of acetylcholinesterase is depends on the type of pesticide ingested⁽⁵⁴⁾. Oximes are recommended by WHO for all symptomatic patients who requires atropine ⁽⁵⁵⁾. Initially a loading dose is given (pralidoxime chloride or obidoxime) to attain therapeutic concentration followed by continuous infusion. When oxime loading dose is given as bolus as rapidly they can cause vomiting which can lead to aspiration ,also can cause diastolic hypertension and tachycardia.⁽⁵⁶⁾.

In OPC intoxication Pralidoxime should be given as 500 mg/hr continuous infusion till patients clinical pattern improves or 30 mg / kg IV bolus for 4–6 h or 8–10 mg /kg / hr IV till clinical improvement & recovery .

PAM dose for children are 25 mg/kg IV for 15 to 30 min followed by continuous IV infusion of 10 to 20 mg / kg / hour In paediatric group.PAM can be infused till clinical recovery or upto 18 hours based on clinical situation⁽⁵⁷⁾.

Obidoxime:

Obidoxime was given to volunteers by IM .The dose of 5 mg / kg brings a serum level of >4 mg/L when 5mg /kg is given (5min after injection to 3 hr). Adverse reactions includes sore throat headache ,generalized weakness, nausea, pallor, burning sensation, and numbness of the face. After higher doses of grams per day in severely poisoned individuals, increased serum transaminases, jaundice and cholestasis like hepatotoxic features observed occasionally⁽⁵⁸⁾.

Dose of obidoxime in adults is 250mg slow IV , after that continuous IV infusion of 750 mg / day, to attain a serum level of 10–20 $\mu\text{mol} / \text{L}$, 0.4 mg/kg /hr should be given. Obidoxime can be given IM when IV access is impossible. Paediatric dose of obidoxime is 3 to 6 mg / kg slow IV over 5min⁽⁵⁷⁾.

Asoxime (HI-6):

It can be given as 500 mg or 250 mg IM.The plasma concentration reaches >4 mg / L after five minutes of IM route. When 500 mg was given the

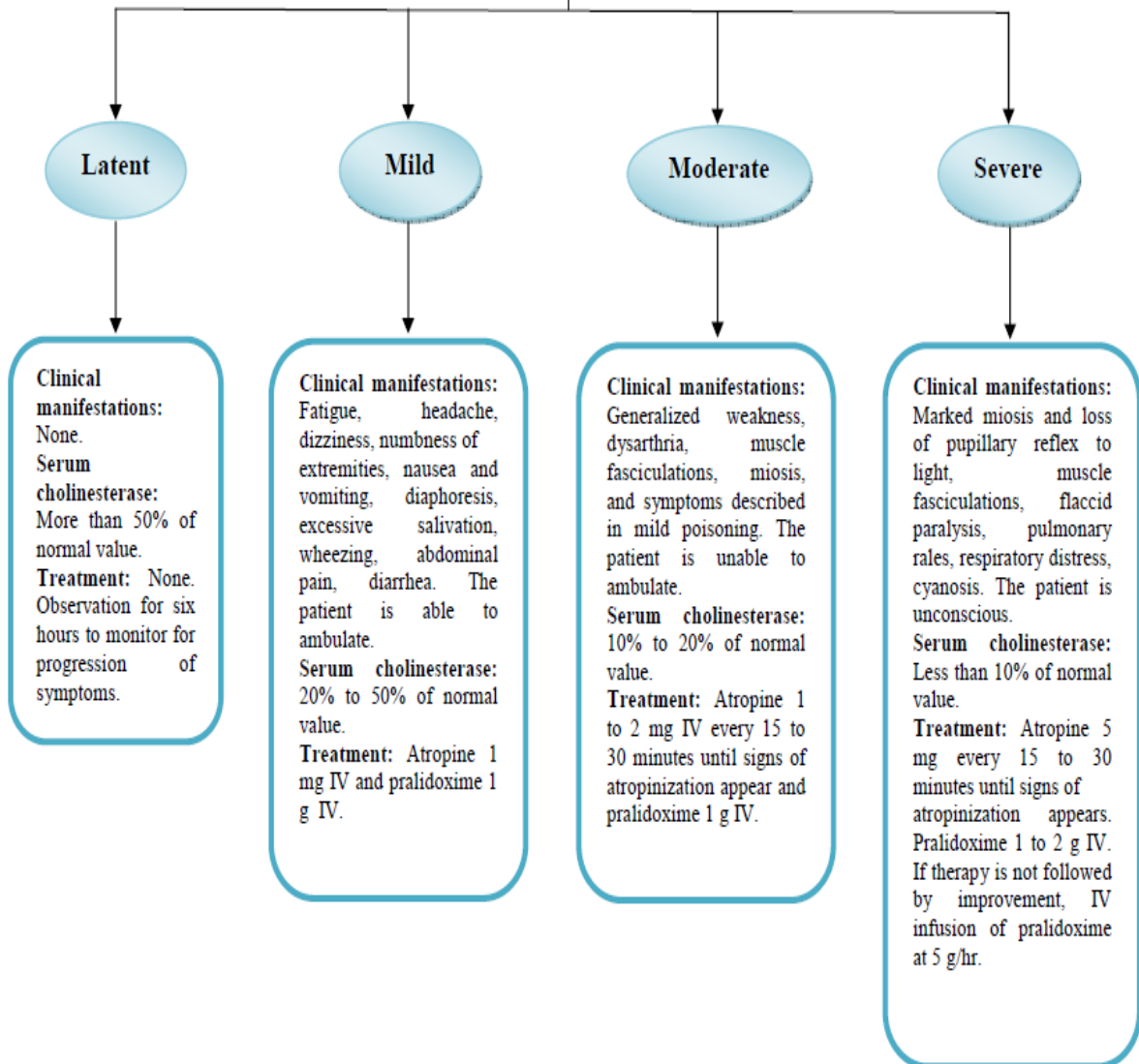
plasma concentration was maintained upto 200 minutes, when 250 mg injected the concentration was maintained upto 125 minutes. It was given as 500 mg 6th hourly IM with atropine. Diazepam was also concurrently given.

Continuation of oxime therapy should be upto 2-7 days depending upon clinical status.

22 healthy human volunteers was given HI-6 500 mg by orally, there was no adverse reactions following nerve agents intoxications HI-6 (bispyridinium oxime) works well as a treatment modality. The drawback of HI-6 as compared to other oximes is its unstable nature in aqueous formulations. In OPC compound poisoning HI-6 was an successful antagonist in combination with atropine & diazepam in therapy⁽⁵⁸⁾.

Oximes are ineffective when complications occur after OPC especially with rapid acting agents like dichlorvos and parathion ⁽⁵⁹⁾.

POISONING



Challenges commonly encountered in treatment of OP Compounds

- 1) Inadequacy of Forensic labs in Government setup
- 2) Lack of toxicology Information Centres.
- 3) Lack of education regarding use of pesticides.
- 4) Inadequacy of health care professionals in studies regarding poison
- 4) Unavailability of newer antidotes.
- 5) Easy availability of OP compounds (especially pesticides) in the market. 6)
- Indeterminate quantitative estimation in patients.
- 7) Increased rate of respiratory failure
- 8) Increasing incidence of diaphragmatic palsy.
- 9) Increased exposure and or consumption leads to development of hemorrhagic pancreatitis.
- 10) Increased use of pesticides raises health hazard in people leading to reduction in GDP.

Prevention of OP Poisoning:

1. It is better to prevent rather than to treat the patient because of toxicity & treatments risk.
2. Before using pesticides in home make sure that windows and doors are open to allow necessary ventilation.
3. When pesticides are labelled to be used outdoors don't use it in home environment.
4. Follow the instructions & warnings printed in pesticides label's always.
5. Always use products which can be used instantly ,instead of products that require mixing.
6. Don't keep any food material in and around the area of application or keep it covered adequately.
7. Before consuming food materials wash them thoroughly.
8. Dispose the insecticide containers carefully. Don't use them for any other purpose .Even if it is washed thoroughly there will be some insecticide remains in it.
9. Avoid transferring pesticides to other containers, can be mistakenly handled by children.

10. While using insecticide use gloves and other protective clothes.
11. Wash hands after handling pesticides.
12. Ensure regular washing of children's hands throughout the day.
13. Keep the as not reachable to children
14. Educate the children regarding poisons and their ill effects.
15. Dont put pesticides in toilet / drainage system ⁽⁶⁸⁾.

AIMS AND OBJECTIVES

1. To study the clinical profile of myocardial involvement in various organophosphorous compound poisoning.

2. To study prevalence and predictors of outcomes of myocardial injury with Creatine phosphokinase MB as biomarkers in organophosphorous poisoning.
3. To correlate the myocardial injury with the clinical severity and outcome in organophosphorous poisoning.

MATERIALS AND METHODS

PLACE OF STUDY:

Department of general medicine, Intensive medical care ward (IMCW), General Medical Wards, Stanley medical college and hospital, Chennai.

DURATION:

February 2014 to September 2014

STUDY DESIGN

Prospective and observational study

SOURCE OF DATA:

Patients with history of organophosphorous poison consumption who fulfil the inclusion and exclusion criteria, getting admitted at stanley medical college chennai, during the period of February 2014 to September 2014

SAMPLE SIZE :

60 patients

INCLUSION CRITERIA:

1. All symptomatic patients having ingested organophosphorous compound with moderate and severe organophosphorous poisoning.

EXCLUSION CRITERIA:

1. Patients who have ingested other substance in addition to op will also be excluded.
2. patients who are known to have pre existing heart disease like rheumatic heart disease, ischemic heart disease etc.
3. Patients who are hypertensive's.
4. Patients who are chronic alcoholics.
5. Patients with chronic kidney disease.
6. Patients who are below the age of 12 years.
7. Patients aged more than 70 years.
8. Patients who are known to have muscular, neuromuscular disease.

METHODOLOGY

Patients admitted with ingestion of organophosphorous compound to the Intensive medical care unit (IMCW) from February 2014 to September 2014 are included in the study. Patients will be subjected to symptom analysis, clinical examination, laboratory investigations. The final analysis will be made at the end of the study to achieve the fore mentioned goals.

Data will be collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations will be undertaken. The purpose of the study will be explained to the patient and informed consent obtained.

Using non-invasive methods cardiac injury in organophosphorous poisoning who fulfil the inclusion criteria are assessed and also analyse the cardiac enzyme levels with the outcome of the patient.

Patients are classified into three grades using “Peradeniya organophosphorous poisoning scale”.

Changes in ECG will be monitored and serum Creatine phosphokinase – MB, serum cholinesterase levels will be measured at admission and repeated on third day and seventh day or at discharge. If the stay is more than seven days they are tested on alternate days till discharge, and taken for analysis.

The course of acute cardiac injury and enzyme levels in organophosphorous poisoning and its effect on the prognosis will be assessed.

CPK –MB level of >40 U/L is considered to have a significant association with cardiac injury.

The analysis of the data will be done using appropriate statistical methods.

Clinical severity is assessed by Peradeniya scoring system and it is used to compare with other parameters of the study.

PERADENIYA SCORE

This scale includes patients who attended hospital within 24 hrs of consumption of poisoning without any medical intervention. This criteria is based on patients at the time of admission and classified as mild moderate and severe poisoning. As per our goals blood samples are sent. Full recovery and death are considered as end points.

RESULTS AND DISCUSSION

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analysed with the Unpaired t test/Anova and categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using EpiInfo software (7.1.0.6 version; Center for disease control, USA) and Microsoft Excel 2010.

Sample Size Calculation

Sample size was determined on the basis of a pilot study in which the prevalence of death among organophosphorous poisoning patients was measured at 4%. We calculated a minimum sample size of 59 patients was required, assuming a type 1 error (two-tailed) of 0.05 and a margin of error of 10%. Therefore, the final sample selected was $n = 60$.

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

Description:

n = required sample size

t = confidence level at 95% (standard value of 1.96)

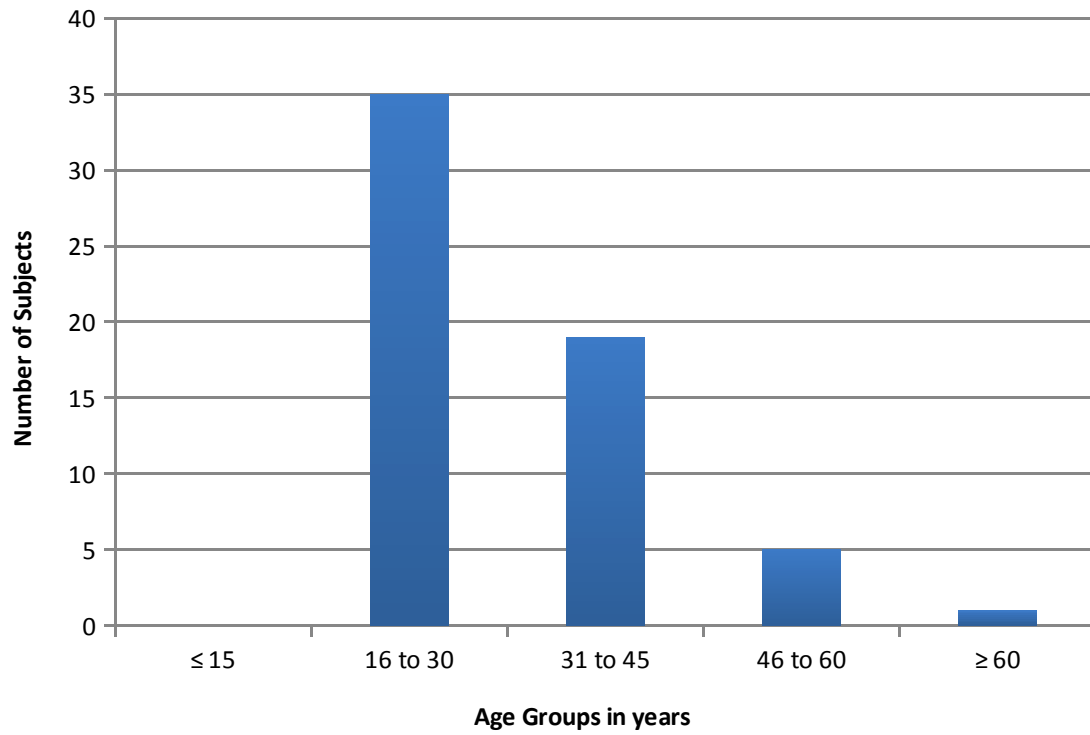
p = estimated prevalence of malnutrition in the project area

m = margin of error at 10% (standard value of 0.05)

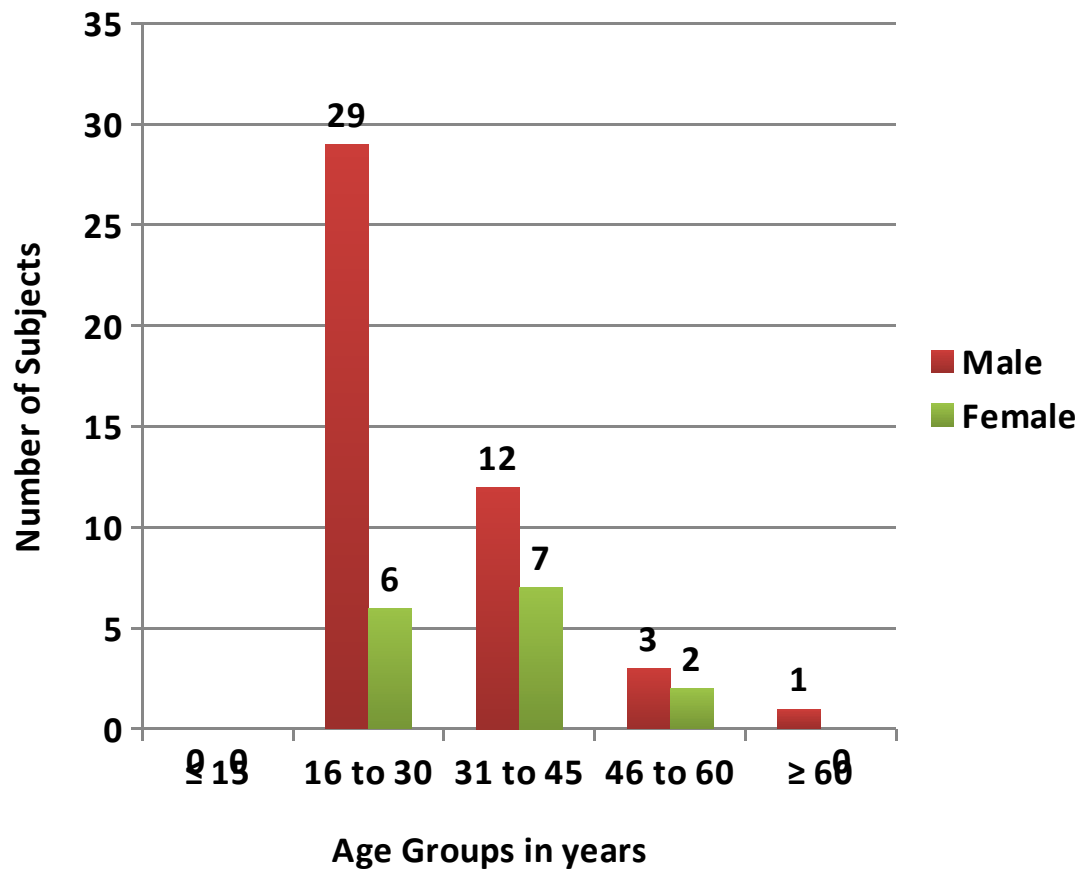
$$n = \frac{(1.96)^2 \times 0.04(1-0.865)}{(0.05)^2}$$

$$\begin{aligned} n &= \frac{3.8146 \times 0.0384}{0.0025} \\ &= 59 \\ &= 60 \text{ in the study group} \end{aligned}$$

Age Distribution



Age Distribution based on Gender

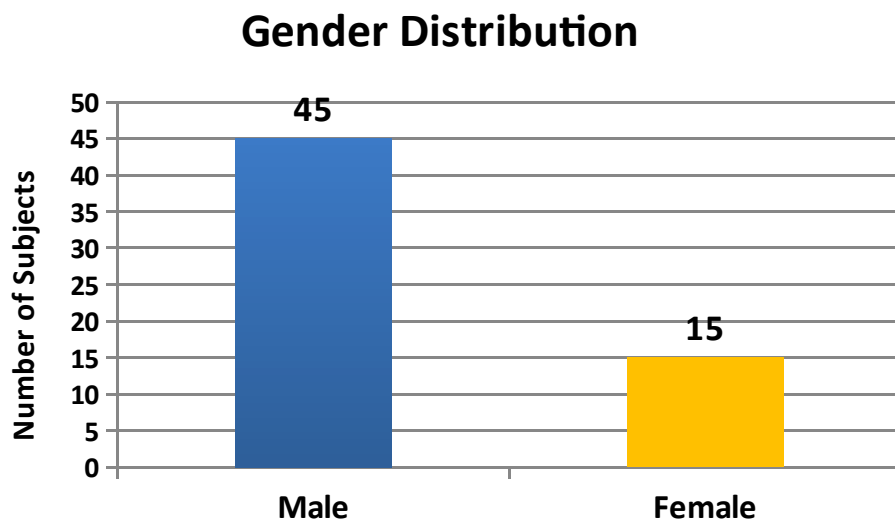


Age in Years	All	%	Male	%	Female	%
≤ 15	0	0.00	0	0.00	0	0.00
16 to 30	35	58.33	29	64.44	6	40.00
31 to 45	19	31.67	12	26.67	7	46.67
46 to 60	5	8.33	3	6.67	2	13.33
≥ 60	1	1.67	1	2.22	0	0.00
Total	60	100	45	100	15	100

AGE	
N	60
Mean	30.15
SD	11.01128
P value One sample t test	0.1002

By conventional criteria the study variable age is considered to be not statistically significant since $p > 0.05$.

Gender

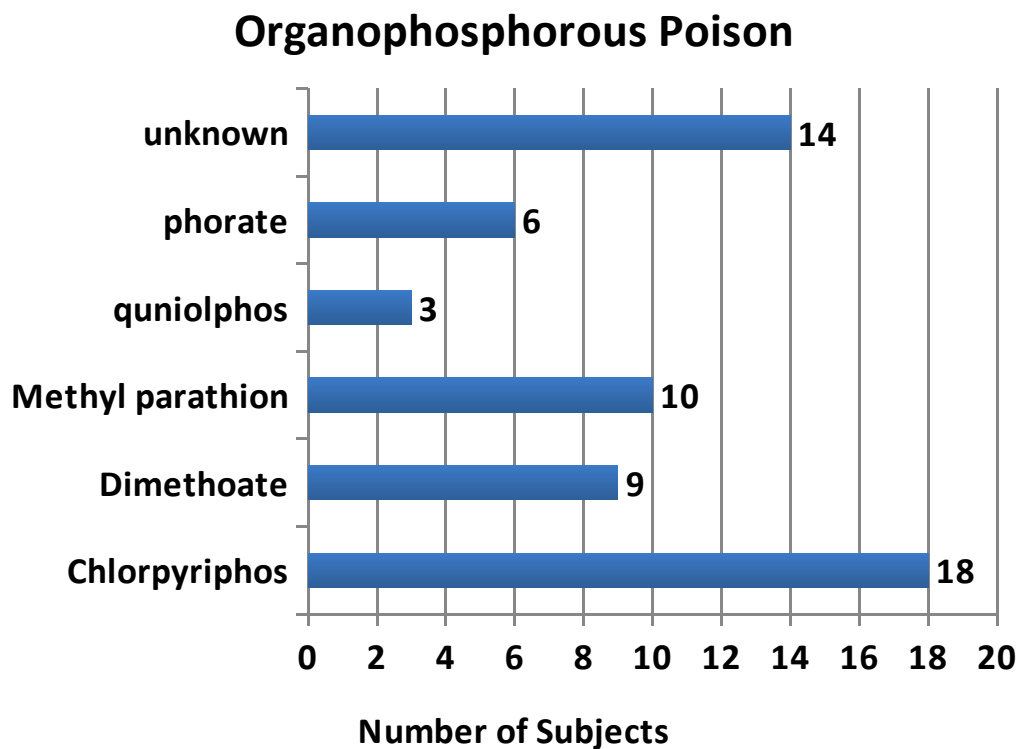


Gender Distribution	Number of Observations	%
Male	45	75
Female	15	25
Total	60	100
P value One sample z test for proportions	1.0457	

By conventional criteria the study variable gender is considered to be not statistically significant since $p > 0.05$.

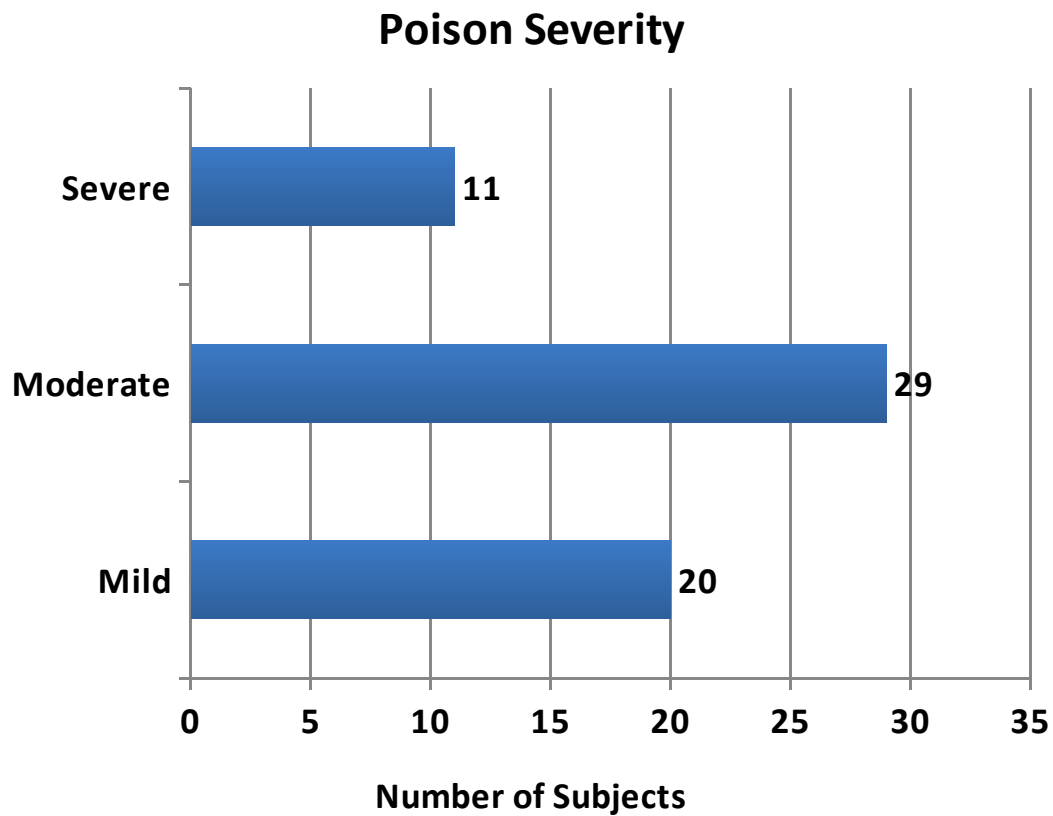
Since age and gender is not statistically significant, it means that there is no difference between the groups. In other words the groups contain subjects with the same basic demographic characteristics.

ORGANOPHOSPHOROUS POISON



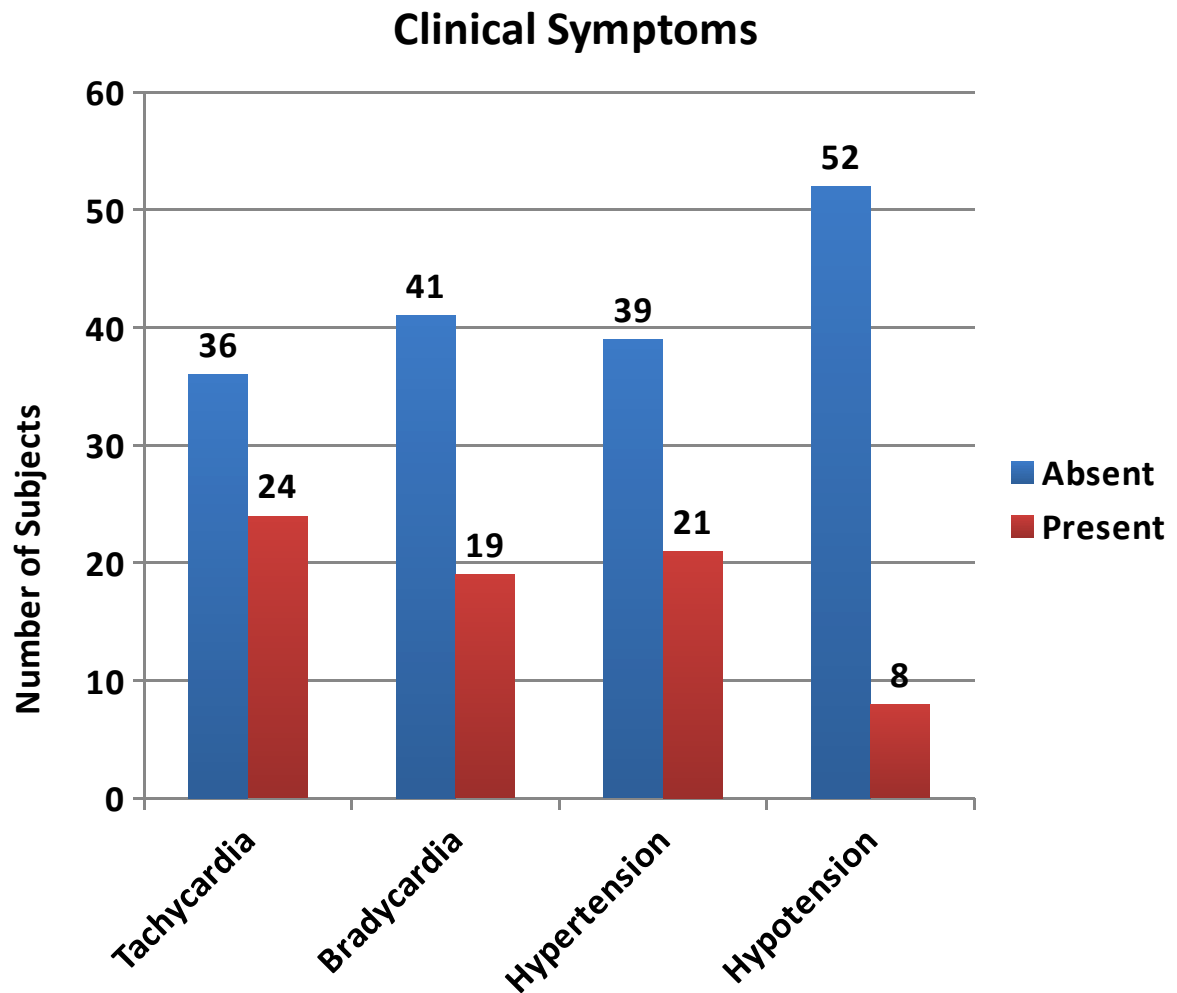
Organophosphorous Poison	N	%
Chlorpyriphos	18	30.00
Dimethoate	9	15.00
Methyl parathion	10	16.67
quniolphos	3	5.00
phorate	6	10.00
unknown	14	23.33
Total	60	100

POISON SEVERITY



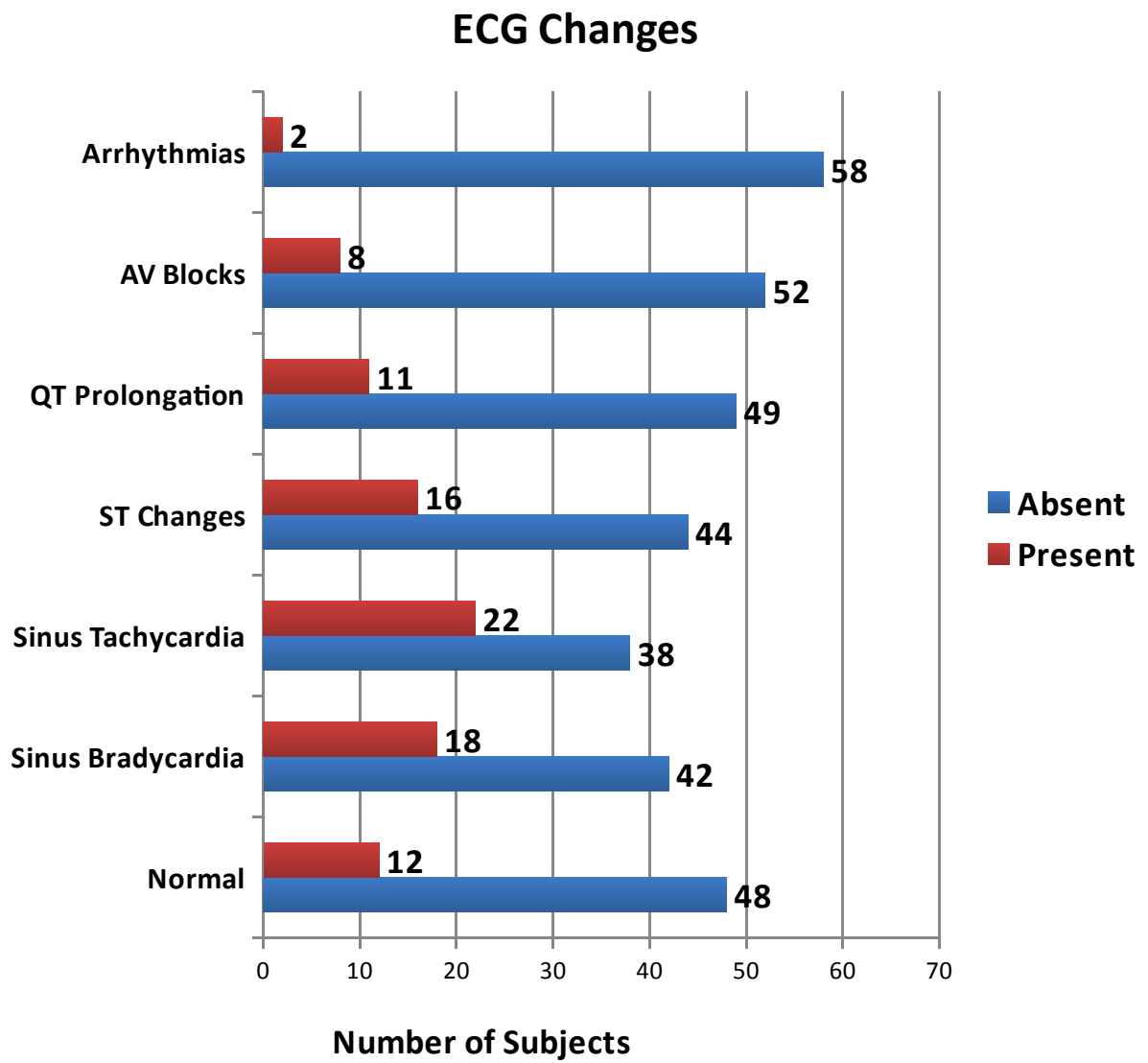
Poison Severity	N	%
Mild	20	33.33
Moderate	29	48.33
Severe	11	18.33
Total	60	100

CLINICAL SYMPTOMS

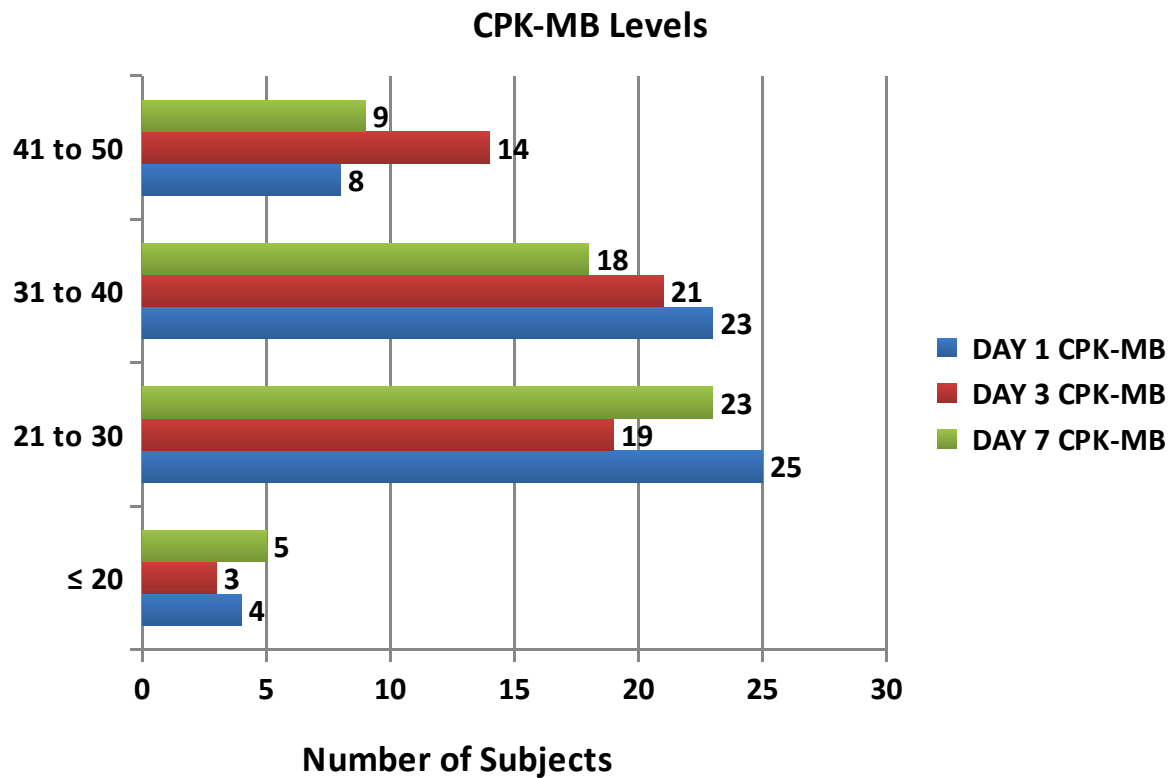


Clinical Symptom	Tachycardi	%	Bradycardi	%	Hypertensio	%	Hypotensio	%
	a		a		n		n	
Absent	36	60.00	41	68.33	39	65.00	52	86.67
Present	24	40.00	19	31.67	21	35.00	8	13.33
Total	60	100	60	100	60	100	60	100

ECG Changes



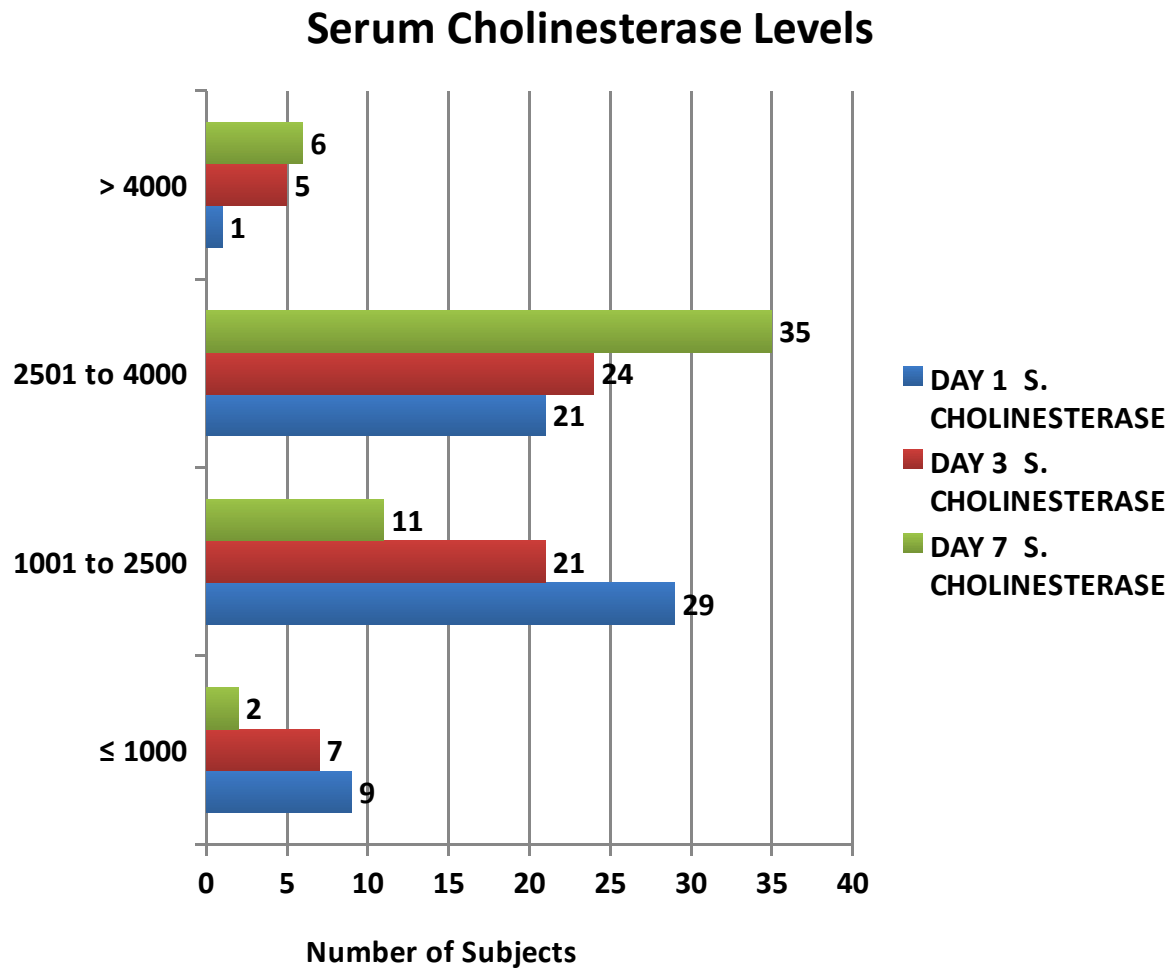
ECG Changes	Normal		Sinus Bradycardia		Sinus Tachycardia		ST Changes		QT Prolongation		AV Blocks		Arrhythmias	
		%		%		%		%		%		%		%
Absent	48	80.0	42	70.0	38	63.3	44	73.3	49	81.6	52	86.6	58	96.6
Present	12	20.0	18	30.0	22	36.6	16	26.6	11	18.3	8	13.3	2	3.33
Total	60	100	60	100	60	100	60	100	60	100	60	100	60	100



CPK-MB	DAY 1 CPK-MB	%	DAY 3 CPK-MB	%	DAY 7 CPK-MB	%
≤ 20	4	6.666667	3	5.263158	5	9.090909
21 to 30	25	41.66667	19	33.33333	23	41.81818
31 to 40	23	38.33333	21	36.84211	18	32.72727
41 to 50	8	13.33333	14	24.5614	9	16.36364
Total	60	100	57	100	55	100

CPK-MB	DAY 1 CPK-MB	DAY 3 CPK-MB	DAY 7 CPK-MB
N	60	57	55
Mean	30.93333	32.21053	30.38182
SD	7.848284	8.741385	9.288294

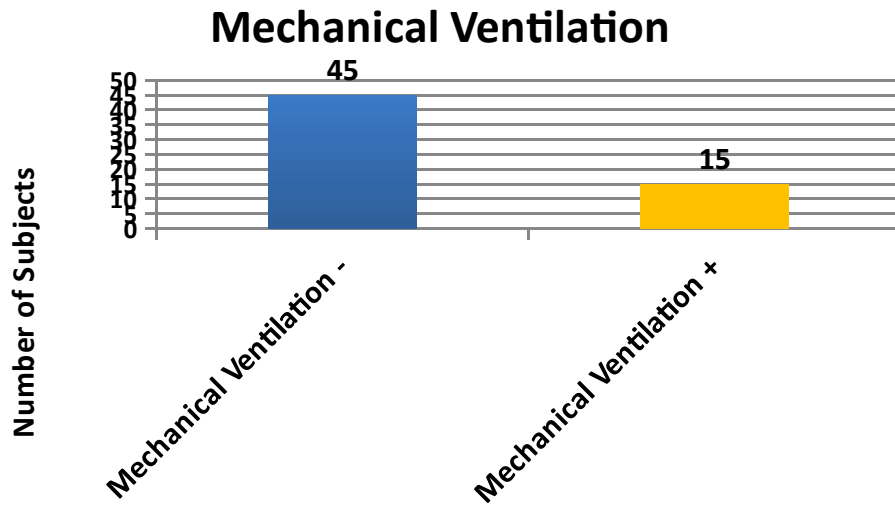
SERUM CHOLINESTERASE



Serum Cholinesterase	DAY 1 S. CHOLINESTERASE	%	DAY 3 S. CHOLINESTERASE	%	DAY 7 S. CHOLINESTERASE	%
≤ 20	9	15.0	7	12.28	2	3.70
21 to 30	29	48.3	21	36.84	11	20.3
31 to 40	21	35.0	24	42.11	35	64.8
41 to 50	1	1.67	5	8.77	6	11.1
Total	60	100	57	100	54	100

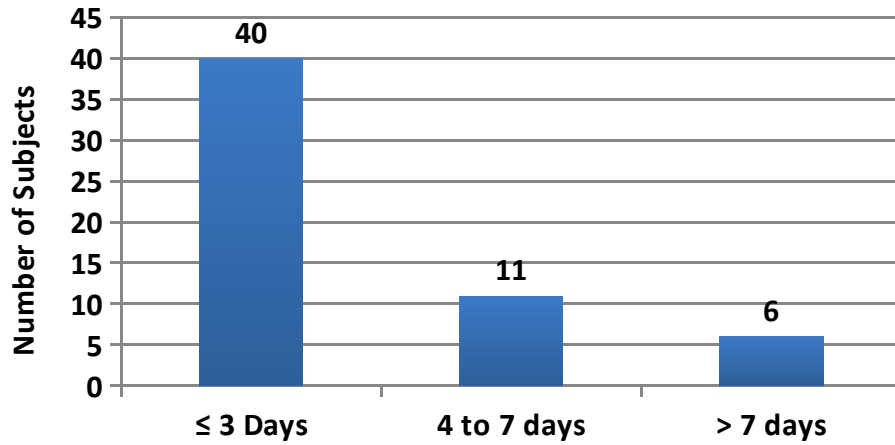
Serum Cholinesterase	DAY 1 S. CHOLINESTERASE	DAY 3 S. CHOLINESTERASE	DAY 7 S. CHOLINESTERASE
N	60	57	54
Mean	2176.95	2520.772	3438.241
SD	921.0435	1063.572	4028.406

Mechanical Ventilation



Mechanical Ventilation	Number of Observations	%
Mechanical Ventilation -	45	75
Mechanical Ventilation +	15	25
Total	60	100

ICU Stay Duration

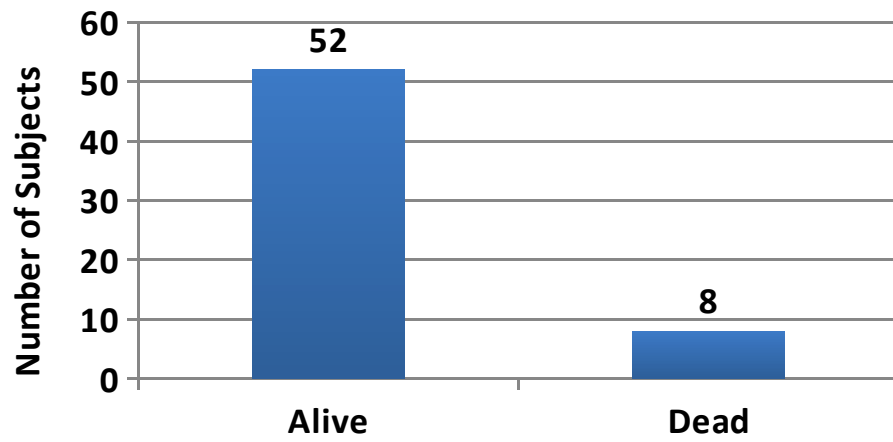


ICU Stay	N	%
≤ 3 Days	40	70.18
4 to 7 days	11	19.30
> 7 days	6	10.53
Total	57	100

	ICU Stay
N	57
Mean	3.245614
SD	2.230316

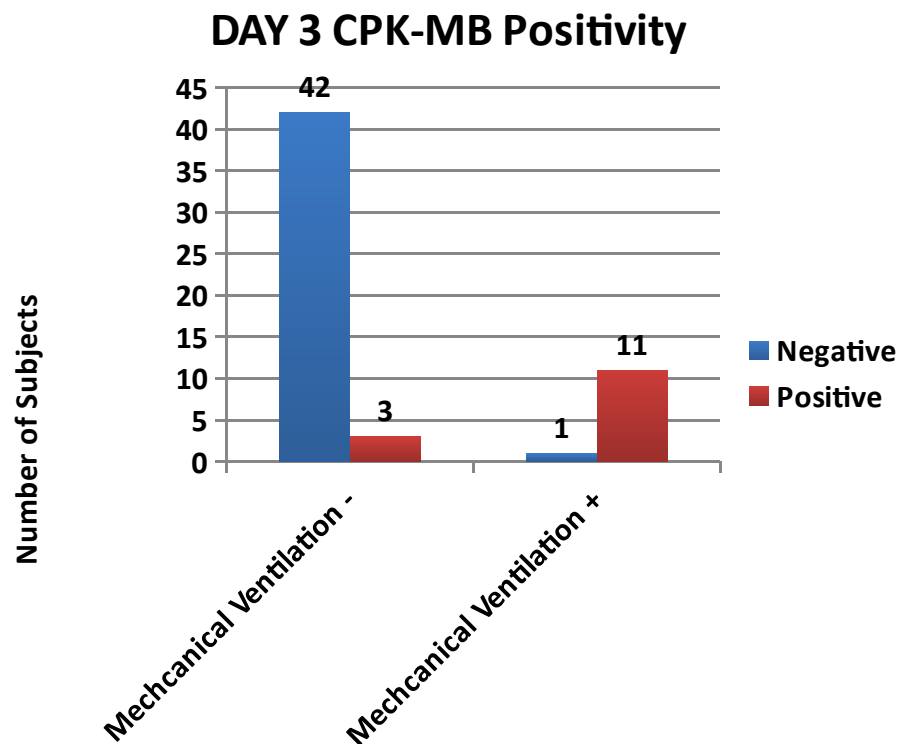
Treatment Outcome

Treatment Outcome



Outcome	N	%
Alive	52	86.67
Dead	8	13.33
Total	60	100

DAY 3 CPK-MB POSITIVITY



DAY 3 CPK-MB Positivity	Mechanical Ventilation -	%	Mechanical Ventilation +	%
Negative	42	93.33	1	8.33
Positive	3	6.67	11	91.67
Total	45	100	12	100
Chi square statistic	36.9			
Degrees of freedom	1			
P value Chi squared test	0.000			

By conventional criteria the association between DAY 3 CPK-MB Positivity and respiratory depression is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying myocardial injury in organophosphorous compound poisoning, the incidence DAY 3 CPK-MB Positivity 3 in patients without respiratory depression and 11 in patients with respiratory depression with a p-value of 0.000 according to Chi-Squared test.

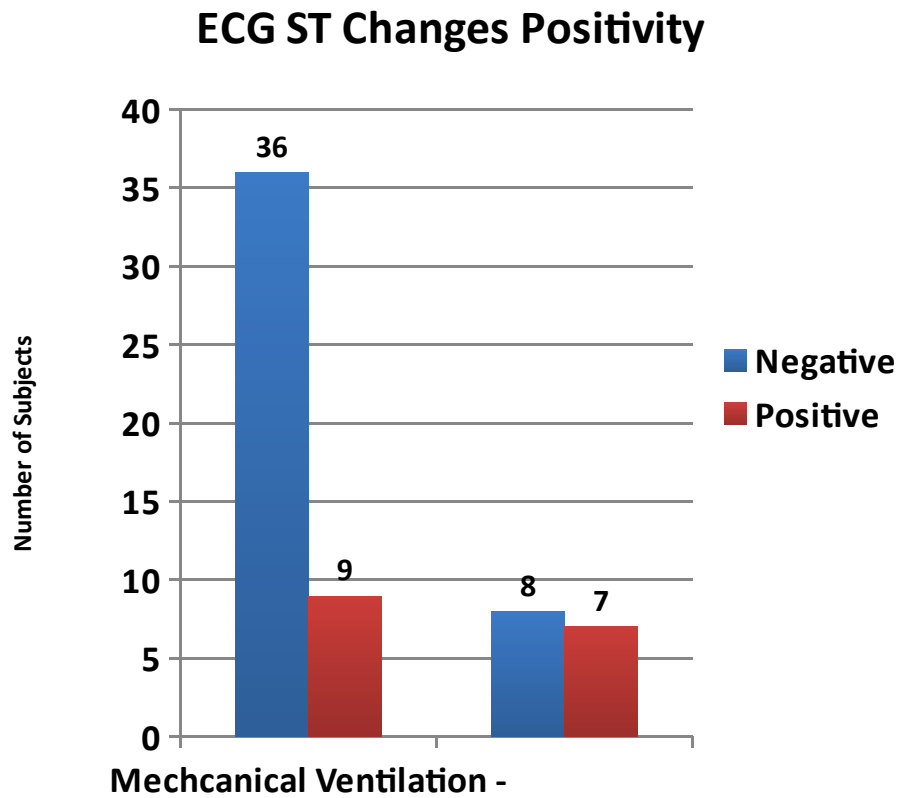
Clinical Significance

The incidence of DAY 3 CPK-MB Positivity among patients treated for myocardial injury in organophosphorous compound poisoning was meaningfully less(6.67%) in patients without respiratory depression compared to patients with respiratory depression (91.67%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is real advantage if the patient is classified based on DAY 3 CPK-MB Positivity, which in turn increases the risk of having respiratory depression. This also proves there is an increasing trend of respiratory depression with DAY 3 CPK-MB Positivity.

ECG ST Change Positivity



ECG ST Change Positivity	Mechanical Ventilation -	%	Mechanical Ventilation +	%
Negative	36	80.00	8	53.33
Positive	9	20.00	7	46.67
Total	45	100	15	100
Chi square statistic	4.09			
Degrees of freedom	1			
P value Chi squared test	0.043			

By conventional criteria the association between ECG ST Change Positivity and respiratory depression is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant. In simple terms, while studying myocardial injury in organophosphorous compound poisoning, the incidence ECG ST Change Positivity 9 in patients without respiratory depression and 7 in patients with respiratory depression with a p-value of 0.043 according to Chi-Squared test.

Clinical Significance

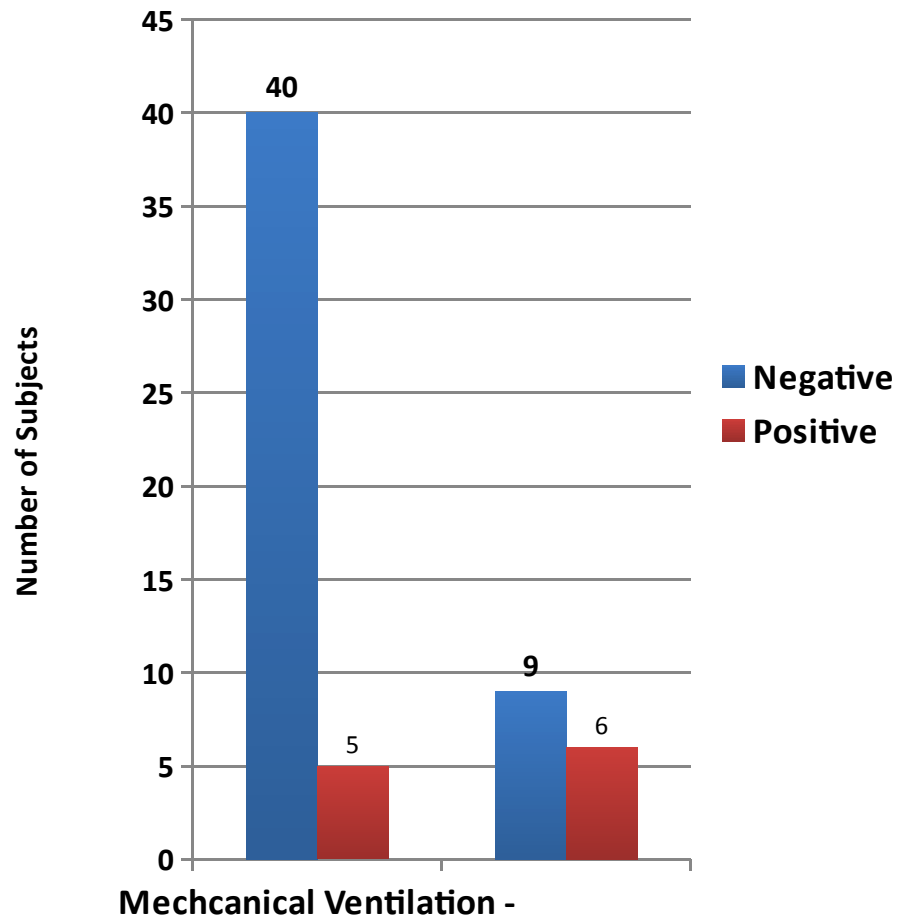
The incidence ECG ST Change Positivity among patients treated for myocardial injury in organophosphorous compound poisoning was meaningfully less(20%) in patients without respiratory depression compared to patients with respiratory depression (46.67%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is real advantage if the patient is classified based on ECG ST Change Positivity, which in turn increases the risk of having respiratory depression. This also proves there is an increasing trend of respiratory depression with ECG ST Change Positivity.

ECG QT PROLONGATION POSITIVITY

ECG QT Prolongation Positivity



ECG QT Prolongation Positivity	Mechanical Ventilation -	%	Mechanical Ventilation +	%
Negative	40	88.89	9	60.00
Positive	5	11.11	6	40.00
Total	45	100	15	100
Chi square statistic	6.27			
Degrees of freedom	1			
P value Chi squared test	0.012			

By conventional criteria the association between ECG QT Prolongation Positivity and respiratory depression is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying myocardial injury in organophosphorous compound poisoning, the incidence ECG QT Prolongation Positivity 5 in patients without respiratory depression and 6 in patients with respiratory depression with a p-value of 0.012 according to Chi-Squared test.

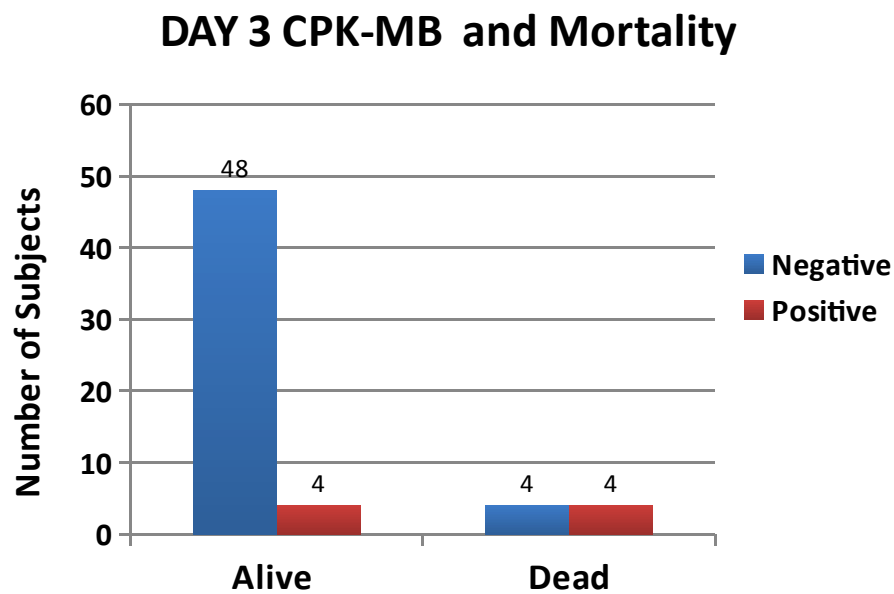
Clinical Significance

The incidence ECG QT Prolongation Positivity among patients treated for myocardial injury in organophosphorous compound poisoning was meaningfully less(11.11%) in patients without respiratory depression compared to patients with respiratory depression (40.00%). This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is real advantage if the patient is classified based on ECG QT Prolongation Positivity, which in turn increases the risk of having respiratory depression. This also proves there is an increasing trend of respiratory depression with ECG QT Prolongation Positivity.

DAY 3 CPK-MB AND MORTALITY



DAY 3 CPK-MB and Mortality	Mortality -	%	Mortality +	%
Negative	48	92.31	4	50.00
Positive	4	7.69	4	50.00
Total	52	100	8	100
Chi square statistic	10.7			
Degrees of freedom	1			
P value Chi squared test	0.001			

By conventional criteria the association between DAY 3 CPK-MB Positivity and mortality is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying myocardial injury in organophosphorous compound poisoning, the incidence DAY 3 CPK-MB Positivity 4 in patients alive and 4 in patients dead with a p-value of 0.001 according to Chi-Squared test.

Clinical Significance

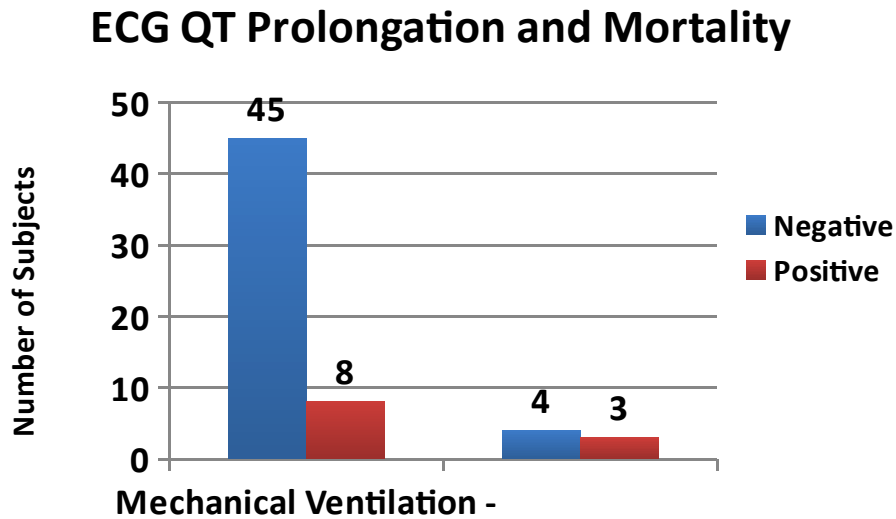
The incidence of DAY 3 CPK-MB Positivity among patients treated for myocardial injury in organophosphorous compound poisoning was meaningfully less(7.69%) in patients alive compared to patients dead (50%).

This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is real advantage if the patient is classified based on DAY 3 CPK-MB Positivity, which in turn increases the risk of death. This also proves there is an increasing trend of mortality with DAY 3 CPK-MB Positivity.

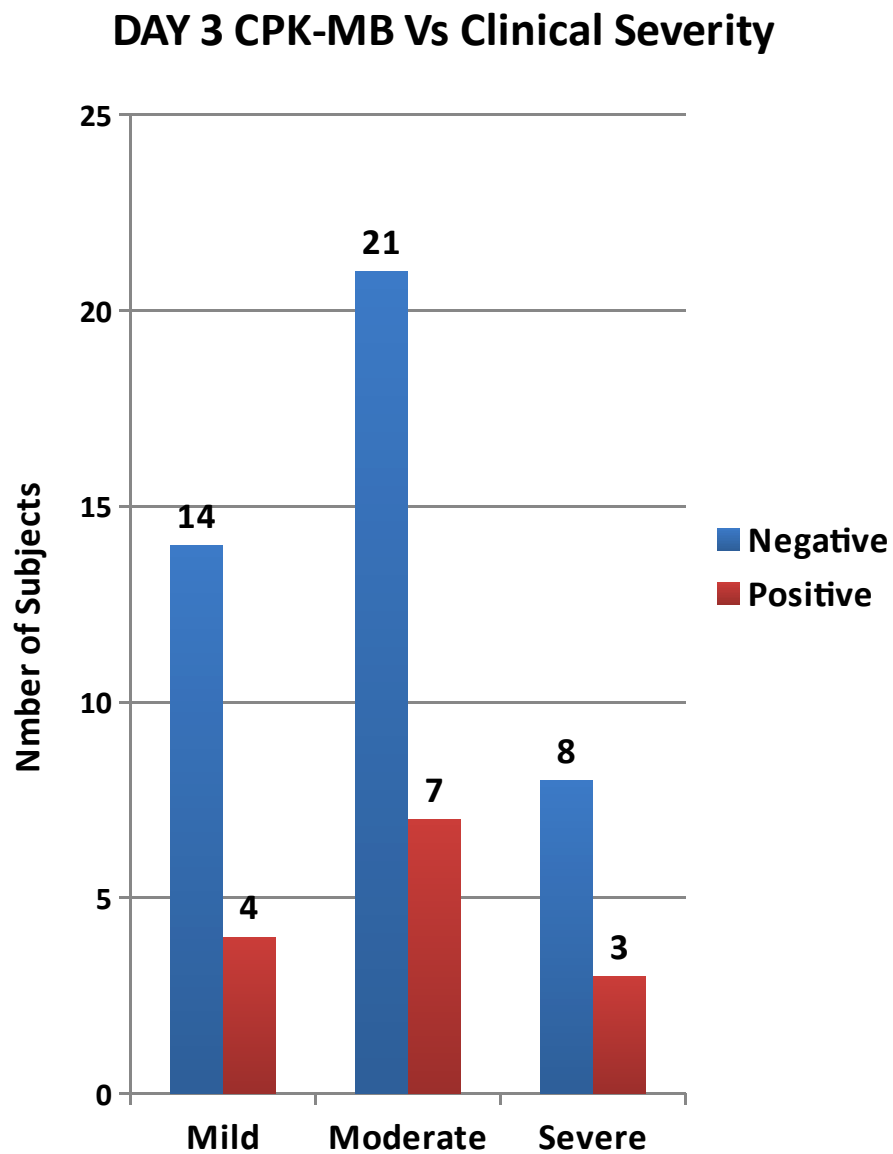
ECG QT Prolongation and Mortality



ECG QT Prolongation and Mortality	Mortality -	%	Mortality +	%
Negative	45	84.91	4	57.14
Positive	8	15.09	3	42.86
Total	53	100	7	100
Chi square statistic	3.18			
Degrees of freedom	1			
P value Chi squared test	0.074			

By conventional criteria the association between ECG QT Prolongation Positivity and mortality is considered to be not statistically significant since $p > 0.05$.

DAY 3 CPK-MB VS CLINICAL SEVERITY

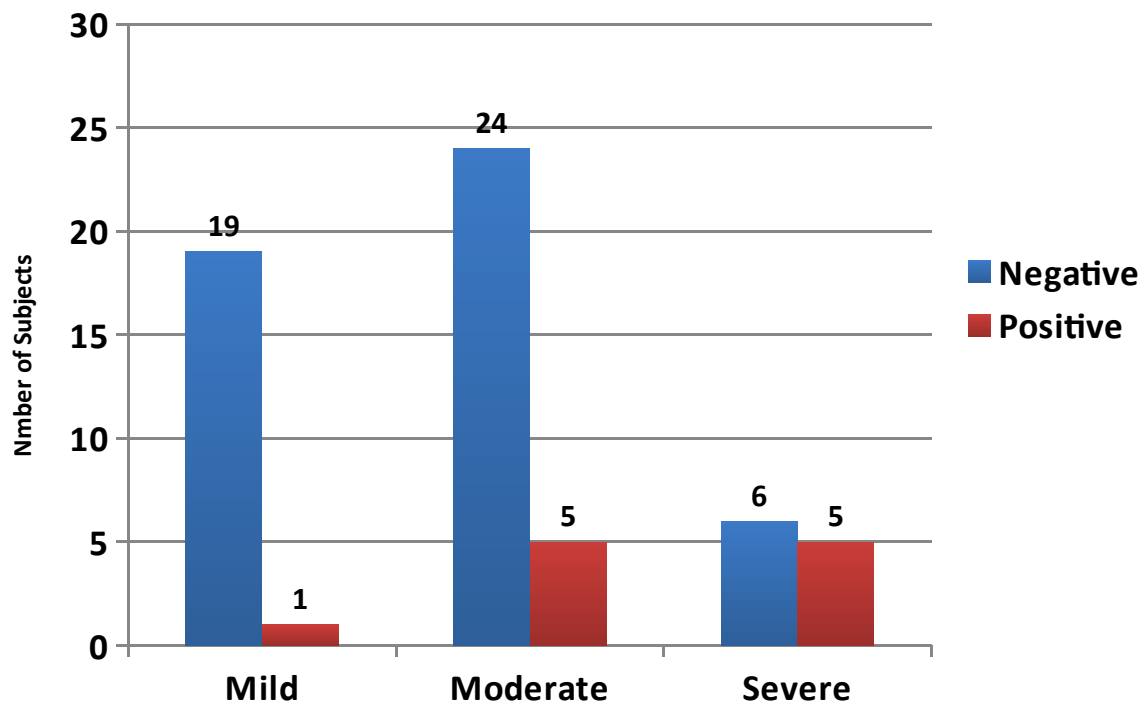


DAY 3 CPK-MB Vs Clinical Severity	Mild	%	Moderate	%	Severe	%
Negative	14	77.78	21	75.00	8	72.73
Positive	4	22.22	7	25.00	3	27.27
Total	18	100	28	100	11	100
Chi square statistic	0.99					
Degrees of freedom	2					
P value Chi squared test	0.951					

By conventional criteria the association between DAY 3 CPK-MB Positivity and clinical severity is considered to be statistically not significant since $p > 0.05$.

ECG QT PROLONGATION VS CLINICAL SEVERITY

ECG QT Prolongation Vs Clinical Severity



ECG QT Prolongation Vs Clinical Severity	Mild	%	Moderate	%	Severe	%
Negative	19	95.00	24	82.76	6	54.55
Positive	1	5.00	5	17.24	5	45.45
Total	20	100	29	100	11	100
Chi square statistic	7.80					
Degrees of freedom	2					
P value Chi squared test	0.020					

By conventional criteria the association between ECG QT Prolongation and Clinical Severity is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while studying myocardial injury in organophosphorous compound poisoning, the incidence ECG QT Prolongation Positivity⁵ in patients with mild clinical symptoms and 5 in patients with moderate clinical symptoms and 5 in patients with severe clinical symptoms with a p-value of 0.020 according to Chi-Squared test.

Clinical Significance

The incidence of ECG QT Prolongation Positivity among patients treated for myocardial injury in organophosphorous compound poisoning was meaningfully less(5.00%) in patients mild clinical symptoms and 17.24% in patients with moderate clinical symptoms and 45.45% in patients with severe clinical symptoms/ This difference is true and significant and has not occurred by chance.

Conclusion

We conclude that there is real advantage if the patient is classified based on ECG QT Prolongation Positivity, which in turn increases the level of clinical symptoms experienced. This also proves there is an increasing trend of clinical severity with ECG QT Prolongation Positivity.

CITATIONS

1)Sadeesh et al &

2)Balouch et al studied electrocardiographic changes in OP compound poisoning the results comparing the two studies are below

	Sadeesh et al	Balouch et al
ST elevation	10.3 %	24 %
Q-T prolgtation	17.2 %	67 %
Sinus tachycardia	12.6%	35 %
Sinus bradycardia	14.9%	28 %

3) Morteza Rahbar Taromsari et al in 2012 studied cardiac injury in opo poisoning by ECG changes .In his study 49 had ECG changes.

4) In Rafigh Doost et al in Iran studied 51 patients with OP poisoning, 33 presented electrocardiographic changes. 64.71% of the patients had a prolonged QTc interval . ST-T changes in 11 cases (29.7%), and conduction defects in two cases (5.4%)(sinus bradycardia,sinus tachycardia, atrioventricular arrhythmia, conduction disturbances, prolonged QTc interval, and non-specific changes in ST segment and T wave are studied)

5) Karki et al study reported that sinus tachycardia occurred in 40.5% prolonged QTc interval in 14 cases (37.8%) and of OP compound poisoned patients

- 6) Yurumez et al. reported that sinus tachycardia (in 31.8% cases) & (55.5%) had a prolonged QTc interval.
- 7)Chuang et al. determined that 97 (43.5%) patients had QTc prolongation, and these patients had poor prognosis.
- 8) Jang et al. determined that 67 of 170 patients had QTc prolongation and in their group, mortality rate, respiratory failure rate, and frequency of ventricular premature contractions were significantly higher than those of patients without QTc prolongation .
- 9)Madhu Pankaj, Kavita Krishna reported acute Organophosphorus Poisoning Complicated by Acute Coronary Syndrome in a 30 year old man with fresh ST elevation and elevated CPK –MB levels ,and he was recovered well and discharged. This was published in JAPI 2014 July.

CONCLUSION OF THIS STUDY

We studied myocardial involvement in organophosphorous poisoning with cardiac enzyme levels and ECG changes, organophosphorous is a commonly encountered in Tamil Nadu.

- 60 patients were included in this study out of which 8 people were dead which gives a mortality of 13.33.
- This study showed there is no correlation of poison severity with age or gender
- This study shows that clinically tachycardia is the most common that is 40%, followed by hypertension 35%, bradycardia 31.67% and hypotension 13.33.
- According to changes in ECG the most common finding is sinus tachycardia (36.67%), followed by sinus bradycardia (30%), ST-T Changes (26.67%), QT prolongation (18.33%), A-V Blocks (13.33 %) and arrhythmias in 3.3% of patients.
- There is a positive correlation of respiratory depression with day 3 CPK-MB level and ST-T changes and also with QT Prolongation.
- But it showed negative correlation of QT Prolongation with mortality.
- It also showed negative correlation with day 3 CPK-MB levels with clinical severity.
- QT Prolongation correlates positively with clinical severity

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PROFOMA

NAME :

SL. NO:

AGE /SEX:

OCCUPATION:

ADDRESS WITH CONTACT NUMBER:

IP NO:

DATE OF ADMISSION:

DATE OF DISCHARGE/ DEATH:

HISTORY:

DATE AND TIME OF CONSUMPTION

AMOUNT OF CONSUMPTION

TYPE OF POISONING

NAUSEA /VOMITING

DIARRHEA

SWEATING

INCREASED URINATION

BREATHLESSNESS

CHEST PAIN/PALPITATION

ABDOMINAL PAIN

VISUAL DISTURBANCES/DOUBLE VISION

GIDDINESS

OLIGURIA /ANURIA

SEIZURE

COMA

OTHERS

PHYSICAL EXAMINATION

SENSORIUM

TEMPERATURE

PALLOR

ICTERUS

PEDAL EDEMA

FASCICULATIONS

PUPIL SIZE

SINGLE BREATH COUNT

BP:

PR:

RR

CVS -

RS -

P/A -

CNS –

NEED OF VENTILATOR

DURATION OF MECHANICAL VENTILATION

OUTCOME OF MECHANICAL VENTILATION

TOTAL AMOUNT OF ATROPINE USED

OTHERS

INVESTIGATIONS

CBC – TC

DC

ESR

HB

PLATELETS

BLOOD SUGAR

UREA

SERUM CREATININE

SODIUM
POTASSIUM
CHLORIDE
BICARBONATE

URINE EXAMINATION

TOTAL CPK

CPK-MB LEVEL

SERUM CHOLINESTERASE LEVEL

ECG

OTHERS

GOVT.STANLEY MEDICAL COLLEGE, CHENNAI- 600 001

INFORMED CONSENT

DISSERTATION TOPIC: "A STUDY OF MYOCARDIAL INJURY IN ORGANOPHOSPHOROUS COMPOUND POISONING"

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE, CHENNAI

NAME AND ADDRESS OF PATIENT:

I, _____ have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I understand that I can withdraw from the study at any point of time and even then, I will continue to receive the medical treatment as usual.

I understand that I will not get any payment for taking part in this study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full co-operation for this study.

Name and Address of the Volunteer:

Signature/Thumb impression of the Volunteer

Date:

Witnesses:

(Signature, Name & Address)

Date:

Name and signature of investigator:

Date:

ஆர்கனோபாஸ்பரஸ் பூச்சிக் கொல்லி மருந்தினை உட்கொள்வதால் நோயாளிகளுக்கு ஏற்படும் இருதயநோயின்தன்மை குறித்த ஒரு ஆய்வு

ஆய்வாளர்: **மரு.கிரிதரன்**

முதுநிலைப்பட்டமேற்படிப்புமாணவர்,

பொதுமருத்துவப்பட்டப்படிப்பு.

வழிகாட்டி :பேராசிரியர்மரு.வசந்தி.

பொதுமருத்துவபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

பங்கேற்பாளரின் தகவல் படிவம்

நீங்கள்இந்தஆய்வில்பங்கேற்க அழைக்கப்படுகிறீர்கள். இந்தஆய்வில்பங்கேற்கும்முன்,
இதன்நோக்கத்தையும்
,முறைகளையும்
,இதனால்ஏற்படும்பின்விளைவுகளையும்நீங்கள்அறிந்துகொள்ளஆய்வாளர்அளிக்கும்தகவல் :

உங்களநோயின்வரலாறும்
,உங்களின்முழுஉடல்பரிசோதனையும்தெளிவாகவும்விரிவாகவும்பதிவுசெய்யப்படும்.

இந்தஆய்வின்முடிவுகள்மருத்துவகாரணங்களுக்காகவும்
,மருத்துவகல்விக்காகவும்பயன்படுத்தப்படும்
,இந்தஆய்வுபற்றியசந்தேகங்களுக்குஉரியமுறையில்விளக்கமளிக்கப்படும்
,தங்களைப்பற்றியதகவல்கள்இரகசியமாகபாதுகாக்கப்படும்.

இந்தஆய்வில்இருந்துஎப்போதுவேண்டுமானாலும்தாங்கள்எவ்விதமுன்னறிவிப்பின்றியும்,
எவ்விதசட்டசிக்கலும்இன்றிவிலகிக்கொள்ளலாம்.

இந்தஆய்வில்பங்கேற்குமாறுகேட்டுக்கொள்கிறேன்.

நன்றி,

ஆய்வாளர் கையொப்பம்

(மரு.கிரிதரன்)

நோயாளியின் கையொப்பம்

(பெயர்:)

ஆர்கனோபாஸ்பரஸ் பூச்சிக்கொல்லிமருந்தினை உட்கொள்வதால் நோயாளிகளுக்கு ஏற்படும்
இருதயநோயின் தன்மை குறித்த ஒரு ஆய்வு

ஆய்வாளர்:மரு.கிரிதரன்

முதுநிலைபட்டமேற்படிப்புமாணவர்,

பொதுமருத்துவப்பட்டபடிப்பு.

வழிகாட்டி :பேராசிரியர்மரு.வசந்தி.

பொதுமருத்துவபேராசிரியர்,

அரசுஸ்டான்லிமருத்துவமனை.

சுய ஒப்புதல் படிவம்

பெயர்:

வயது:

உள்ளிருப்புஎண்:

இந்தமருத்துவஆய்வின்விவரங்கள்எனக்குவிளக்கப்பட்டது
.என்னுடையசந்தேகங்களைக்கேட்கவும்,அதற்கானதகுந்தவிளக்கங்களைப்பெறவும்வாய்ப்பளிக்கப்பட்டது.

நான்இவ்வாய்வில்தன்னிச்சையாகத்தான்பங்கேற்கிறேன்

.எந்தகாரணத்தினாலும்

.எந்தகட்டத்திலும்

.எந்தசட்டசிக்கலும்இன்றிஇந்தஆய்விலிருந்துவிலகிக்கொள்ளலாம்என்றும்அறிந்துகொண்டேன் .

நான்ஆய்விலிருந்துவிலகிக்கொண்டாலும்ஆய்வாளர்என்னுடையமருத்துவஅறிக்கைகளைப்பார்ப்பதற்கோ
அல்லதுஉபயோகிக்கவோஎன்அனுமதிதேவையில்லை எனவும்

அறிந்துகொண்டேன்.என்னைப்பற்றியதகவல்கள்இரகசியமாகப்பாதுகாக்கப்படும்என்பதையும்அறிவேன் .

இந்தஆய்வின்மூலம்கிடைக்கும்தகவல்களையும்பரிசோதனைமுடிவுகளையும்

.ஆய்வாளர்அவர்விருப்பத்திற்கேற்பஎவ்விதமாகப்பயன்படுத்திக்கொள்ளவும்

.அதனைபிரசுரிக்கவும்முழுமனதுடன்சம்மதிக்கிறேன் .

இந்தஆய்வில்பங்குகொள்ளஒப்புக்கொள்கிறேன்

.எனக்குகொடுக்கப்பட்டஅறிவுரைகளின்படிநடந்துகொள்வதுடன்,

ஆய்வாளருக்குஉண்மையுடன்இருப்பேன்என்றும்உறுதியளிக்கிறேன்

.என்உடல்நலம்பாதிக்கப்பட்டாலோஅல்லதுவழக்கத்திற்குமாறானநோய்க்குறிதென்பட்டாலோஉடனேஅதை
தைதெரிவிப்பேன் என உறுதிசூறுகிறேன் .

இந்தஆய்வில்எனக்கு எவ்விதமான

பரிசோதனைகளையும்,சிகிச்சைகளையும்மேற்கொள்ளநான்முழுமனதுடன்சம்மதிக்கிறேன் .

இப்படிக்கு

நோயளியின்கையொப்பம்

ஆய்வாளர்கையொப்பம்பெயர்

(மரு.கிரிதரன்.)

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study of Myocardial injury in Organo-phosphorous compound poisoning at Stanley medical college, Chennai

Principal Investigator : Dr. GIRIDHARAN V

Designation : P.G in M.D (General Medicine)

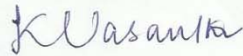
Department : General Medicine

The request for an approval from the Institutional Ethical committee (IEC) was considered on the IEC meeting held on 07.04.2014 at the Council Hall, Stanley Medical College, Chennai 1 at 2 PM

The members of the Committee, the secretary and the Chairman are please to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal Investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of work for which you applied ethical clearance.
3. You should inform the IEC immediately in case of any adverse events or serious adverse reactions
4. You should abide to the rules and regulations of the institution.
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work
6. You should submit the summary of work to the ethical committee on completion of the work.



MEMBER SECRETARY,
IEC, SMC, CHENNAI

KEY TO MASTER CHART

ECG CHANGES

1-NORMAL ECG

2-SINUS TACHYCARDIA

3-SINUS BRADYCARDIA

4-ST-T CHANGES

5-Q-T PROLONGATION

6-A-V BLOCKS

7-ARRHYTHMIAS

M-MALE F-FEMALE

P.SCORE-PERADINEYA SCORE

TACHY-TACHYCARDIA

BRADY-BRADYCARDIA

HT-HYPERTENSION

HYPO-HYPOTENSION

D1-FIRST DAY

D3-THIRD DAY

D7-SEVENTH DAY

CPK-MB-CREATINE PHOSPHOKINASE –MB

S.ChE-SERUM CHOLINESTERASE

MEC.VEN-MECHANICAL VENTILATION

S.NO	AGE	SEX	COMPOUND	P.SCORE	GRADE	TACHY	BRADY	HT	HYPO	ECG CHANGES
1	20	M	Chlorpyriphos	3	MILD	+	-		-	2
2	22	M	Dimethoate	8	SEVERE	-	+		+	4
3	23	M	Methyl parathion	5	MODERATE	+				2
4	17	M	quiniolphos	4	MODERATE	+				2
5	19	M	Methyl parathion	7	MODERATE			+	+	3
6	20	m	Chlorpyriphos	8	SEVERE			+		3,4,5
7	47	F	phorate	5	MODERATE	+		+		4
8	45	M	Dimethoate	5	MODERATE			+		4
9	26	M	quiniolphos	2	MILD					1
10	18	M	Methyl parathion	4	MODERATE	+				2
11	25	M	Chlorpyriphos	1	MILD					1
12	17	M	unknown	4	MODERATE			+		1
13	65	M	Methyl parathion	8	SEVERE			+	+	3
14	30	M	phorate	4	MODERATE	+				2
15	16	M	Dimethoate	4	MODERATE			+		1
16	42	M	Dimethoate	1	MILD					1
17	32	M	Chlorpyriphos	8	SEVERE			+		3,5,6
18	36	F	Chlorpyriphos	0	MILD					1
19	52	F	unknown	5	MODERATE			+		6
20	17	F	Methyl parathion	4	MODERATE	+				2,4
21	19	M	Chlorpyriphos	2	MILD					1
22	27	F	Dimethoate	4	MODERATE	+				2
23	40	F	unknown	1	MILD	+		+		2
24	22	M	unknown	4	MODERATE			+	+	3,4
25	32	M	Chlorpyriphos	5	MODERATE			+	+	3,5
26	40	F	unknown	0	MILD	+				2
27	48	M	Methyl parathion	5	MODERATE	+			+	2,4
28	27	M	Dimethoate	3	MILD	+		+		2
29	26	F	phorate	4	MODERATE			+		3,6
30	23	F	unknown	6	MODERATE			+		3,5
31	32	F	Chlorpyriphos	2	MILD	+				2
32	27	M	Chlorpyriphos	9	SEVERE			-	+	3,4

33	24	M	Dimethoate	0	MILD	+				2
34	20	F	unknown	4	MODERATE		+			3
35	27	M	unknown	3	MILD	+				2
36	45	M	quiniolphos	1	MILD				+	1
37	39	M	phorate	5	MODERATE		+		+	3,5
38	37	M	Chlorpyriphos	8	SEVERE		+		+	3,2,6
39	33	M	s	9	SEVERE		+		+	3,4,5
S.NO	AGE	SEX	COMPOUND	P.SCORE	GRADE	TACHY	BRADY	HT	HYPO	ECG CHANGES
40	19	M	Dimethoate	3	MILD	+				2
41	50	M	unknown	4	MODERATE	+			+	2
42	26	M	Methyl parathion	8	SEVERE		+		+	7
43	25	M	Methyl parathion	5	MODERATE				+	4
44	19	M	phorate	0	MILD					1
45	42	M	Chlorpyriphos	4	MODERATE	+				2,6
46	40	F	Chlorpyriphos	2	MILD				+	5
47	25	M	Chlorpyriphos	8	SEVERE		+			3,4,5,6
48	20	M	s	4	MODERATE	+			+	2,4
49	50	M	unknown	4	MODERATE		+		+	3,5
50	23	M	unknown	3	MILD	+				1
51	16	F	Methyl parathion	2	MILD	+				2
52	40	M	Methyl parathion	4	MODERATE				+	1
53	20	M	Dimethoate	8	SEVERE		+		+	3,4
54	31	F	phorate	4	MODERATE		+			3
55	28	M	Chlorpyriphos	5	MODERATE	+				2,4
56	34	M	s	8	SEVERE		+			3,7
57	21	M	unknown	4	MODERATE	+				2,4
58	30	M	Chlorpyriphos	5	MODERATE	-	-		+	5
59	40	M	unknown	2	MILD	-	-	-	-	1
60	33	F	unknown	3	mild	+	-	-	-	2,4

S.NO	D1-CPK-MB	D3-CPK-MB	D7/DIS-CPK-MB	S.ChE -D1	S.ChE-D3	S.ChE-D 7/DIS	MEC.VEC	NO OF ICU STAY
1	24	22	24	3110	4214	4186	-	
2	35	42	-	750	612	-	+	4
3	29	32	31	2312	3216	3428	-	
4	32	34	32	1980	2564	3196	-	2
5	43	46		1512	890	-	+	3
6	39	42	41	970	1210	1790	+	9
7	28	32	34	1780	2348	2678	-	2
8	34	35	34	1654	1470	1874	-	3
9	18	17	17	2786	3675	4320	-	1
10	22	23	22	2112	3126	2780	-	2
11	23	21	21	3998	4690	4532	-	2
12	34	36	35	1678	2310	3224	-	3
13	39	45	42	480	598	670	+	8
14	31	29	26	1458	1780	2786	-	2
15	25	25	23	2132	2980	3216	-	2
16	23	21	21	3122	3452	3974	-	2
17	48	47	45	798	1578	1764	+	8
18	17	20	19	3453	4512	4124	-	1
19	34	36	35	2345	2348	2872	-	3
20	31	33	32	2678	3248	3424	-	3
21	29	31	29	2570	3120	3086	-	2
22	32	32	31	2018	2676	2692	-	3
23	23	21	22	3458	3890	3638	-	2
24	37	39	39	2234	2118	1560	-	3
25	44	45	44	1782	1340	1642	-	4
26	23	25	26	4340	3890	3586	-	1
27	37	46	45	1674	1560	1982	+	6
28	31	33	32	2784	2876	3128	-	3

29	36	35	36	1982	2312	2874	-	4
30	36	43	42	1120	912	1672	+	6
31	27	28	25	3210	3765	3429	-	1
32	45	-	-	450	-	-	+	4
33	35	32	31	3450	3421	2890	-	1
34	42	43	39	2624	2131	2489	-	4
35	29	31	30	2320	2497	3109	-	2
36	30	31	28	2980	2390	2763	-	1
37	37	42	40	1560	1239	1457	-	3
38	44	47	43	986	678	980	+	9
39	36	41	49	780	430	1252	+	8
40	24	23	26	2442	2347	3428	-	2
41	34	34	35	3210	2789	3120	+	5
42	43	-	-	1260	-	-	+	1
43	36	38	37	2670	2872	2900	-	3
		D3-CPK-			S.ChE-			
S.NO	D1-CPK-MB	MB	D7/DIS-CPK-MB	S.ChE -D1	D3	S.ChE-D 7/DIS	MEC.VEC	NO OF ICU STAY
44	19	21	21	3490	4520	4128	-	1
45	28	34	29	2100	1789	2642	-	3
46	36	38	37	2680	2568	3124	-	4
47	37	48	-	1124	752	-	+	3
48	29	33	37	2168	2453	2876	-	4
49	21	23	22	1560	2789	32100	-	
50	19	21	20	1980	2542	2980	-	2
51	22	23	21	3986	4023	3872	-	1
52	23	21	24	2340	2978	3818	-	3
53	45	-	-	670	-	-	+	2
54	23	24	21	3120	3244	3642	-	3
55	27	28	29	1980	2387	2982	-	4
56	35	43	48	970	1670	2310	+	10
57	22	25	24	2670	3421	3228	-	2
58	29	32	30	1547	2340	2976	-	2
59	21	19	18	2875	3480	3258	-	1
60	21	25	27	2345	2654	3214	-	2

We conclude that this study helps to predict the mortality in organophosphorous poisoning patients with investigations like ECG ,cardiac markers like CPK-MB which are readily available .These simple tools can be used effectively for early intervention and thereby intensifying the treatment which in the long run can reduce the mortality in OPC intoxicated patients.