A Dissertation on

CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME OF ORGANO-PHOSPHOROUS COMPOUND POISONING

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

COIMBATORE

APRIL 2016

CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr. SHALINI M*** *and submitted in partial fulfillment of the requirements for the Degree of* ***M.D.,General Medicine****, Branch I of* ***The TamilnaduDr. M.G.R. Medical University, Chennai.***

Date: **Guide, Professor & Chief**
Medical Unit II

Date: **Professor & Head**
Department of Medicine

Date: **Dean**
Coimbatore Medical College
Coimbatore

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : DR. M. SHALINI.

Course : MD - GENERAL MEDICINE

Period of Study : 2013 - 2016

College : COIMBATORE MEDICAL COLLEGE

Dissertation Topic : CORRELATION OF POP SCALE AND SERUM CHOLINESTRASE LEVEL IN ASSESING THE CLINICAL SEVERITY AND OUTCOME OF ORGIANOPHOSPHORUS COMPOUND POISONING.

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not accepted~~ and you are permitted / ~~Not permitted~~ to proceed with the above Study.

DEAN
Coimbatore Medical College & Hospital, Coimbatore

10.7.2014

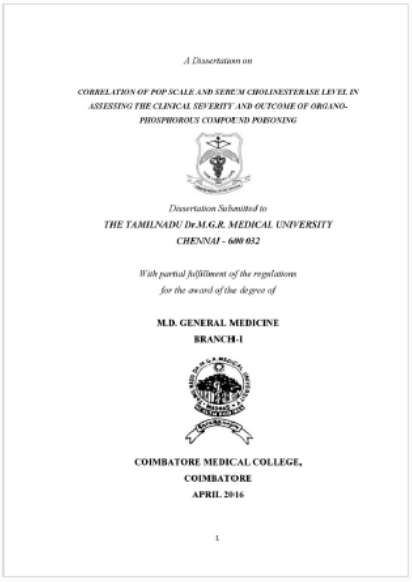
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201311316.md (general Medicine) D..
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	CORRELATION OF POP SCALE AN...
File name:	Shalini_1.6.doc
File size:	3.77M
Page count:	106
Word count:	11,854
Character count:	68,802
Submission date:	17-Sep-2015 12:04AM
Submission ID:	566091635



A Dissertation on

CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME OF ORGANO-PHOSPHOROUS COMPOUND POISONING

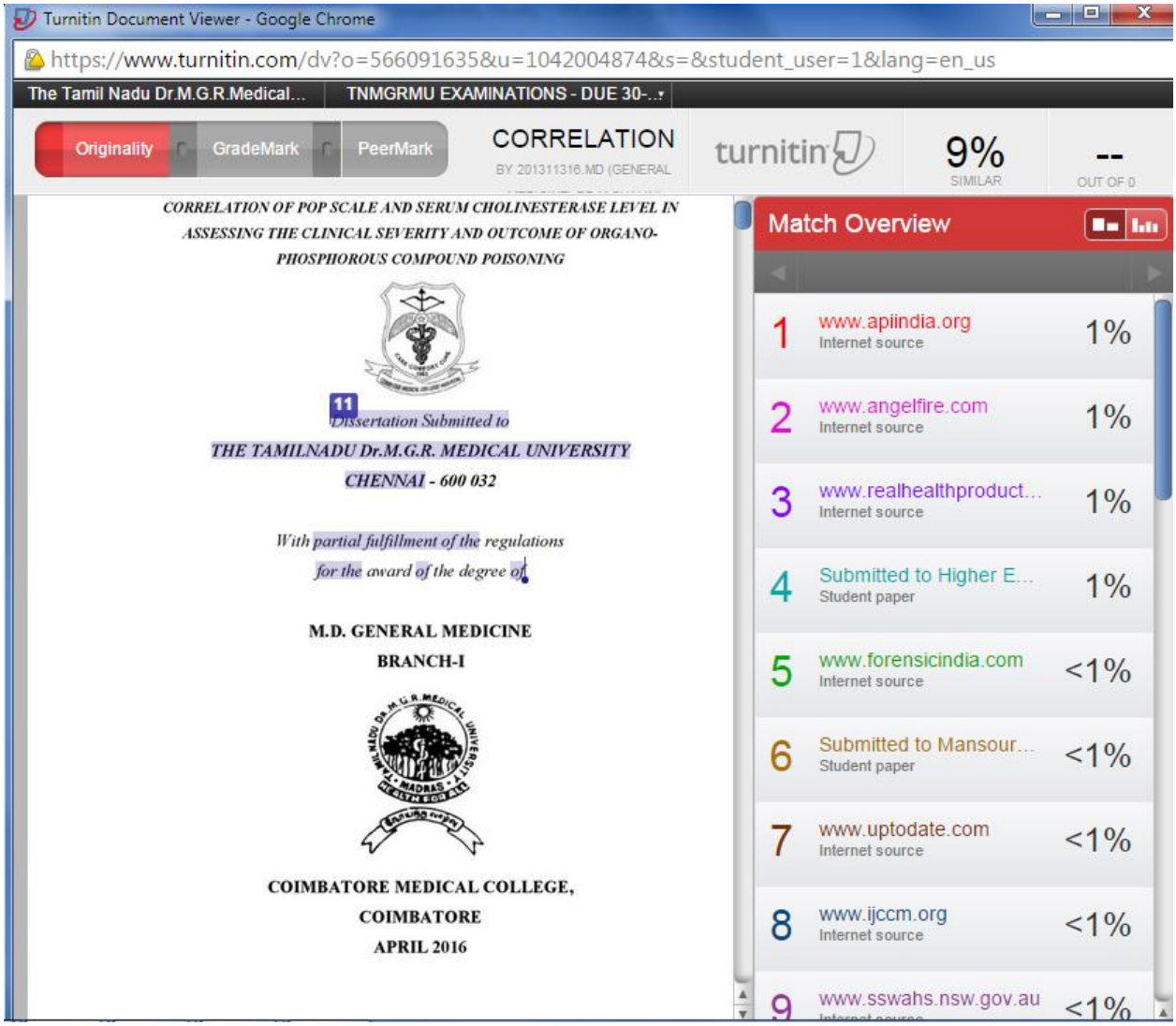
Dissertation Submitted to
THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

With partial fulfillment of the regulations for the award of the degree of

M.D. GENERAL MEDICINE
BRANCH-I

COIMBATORE MEDICAL COLLEGE,
COIMBATORE
APRIL 2016

1


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?o=566091635&u=1042004874&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 30-..
Originality
GradeMark
PeerMark
CORRELATION
BY 201311316.MD (GENERAL
turnitin
9%
SIMILAR
--
OUT OF 0
CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME OF ORGANO-PHOSPHOROUS COMPOUND POISONING
Dissertation Submitted to
THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032
With partial fulfillment of the regulations
for the award of the degree of
M.D. GENERAL MEDICINE
BRANCH-I
COIMBATORE MEDICAL COLLEGE,
COIMBATORE
APRIL 2016
Match Overview
1 www.apiindia.org Internet source 1%
2 www.angelfire.com Internet source 1%
3 www.realhealthproduct... Internet source 1%
4 Submitted to Higher E... Student paper 1%
5 www.forensicindia.com Internet source <1%
6 Submitted to Mansour... Student paper <1%
7 www.uptodate.com Internet source <1%
8 www.ijccm.org Internet source <1%
9 www.sswahs.nsw.gov.au <1%

DECLARATION

I solemnly declare that the dissertation titled **"CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME OF ORGANOPHOSPHOROUS COMPOUND POISONING"** was done by me from JULY 2014 to JUNE 2015 under the guidance and supervision of Professor **Dr.S.USHA. M.D.,**

This dissertation is submitted to **The TamilnaduDr.M.G.R.Medical University** towards the partial fulfilment of the requirement for the award of MD Degree in General Medicine(Branch I).

Place: Coimbatore **Dr. SHALINI M**

Date:

ACKNOWLEDGEMENT

I wish to express my sincere thanks to our respected **Dean Dr.EDWIN JOE,M.D** for having allowed me to conduct this study in our hospital.

I express my heartfelt thanks and deep gratitude to the Head of the Department of Medicine Prof. **Dr.KUMAR NATARAJAN, M.D**. for his generous help and guidance in the course of the study.

I owe a great debt of gratitude to our respected Professor and unit chief Prof.**Dr.S.USHA, M.D** without whose help and advice this work would not have been possible.

I also extend my gratitude to Prof.**Dr.ISAAC CHRISTIAN MOSES, M.D**, and Prof.**Dr.SIVAKUMAR, M.D** Chief, IMCU for his support and expert guidance.

I am extremely grateful to **Dr.MANIMEGALAI, M.D**(Bio), HOD, Department of Biochemistry, for their valuable help and cooperation and allowing me to use institutional facilities.

I sincerely thank all professors and Asst. Professors- **Dr.K.GANESAMOORTHY.M.D, Dr.A.AKILA, M.D, Dr.P.S.RANI, M.D**, for their guidance and kind help.

My sincere thanks to **Dr.S.BALAJI, M.D** Assistant Professor,IMCU and Staff Nurse of Intensive Medical Care Unit for their help.

My sincere thanks to all my friends and post-graduate colleagues for their whole hearted support and companionship during my studies.

I thank all my **PATIENTS**, who formed the backbone of this study without whom this study would not have been possible.

Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering His blessings on me and my family

DATE: **Dr.SHALINI.M**

PLACE:

LIST OF ABBREVIATIONS USED

- **AChE**- Acetylcholinesterase
- **Ach**- Acetylcholine
- **ANS**- Autonomic nervous system
- **BChE**- Butrylcholinesterase
- **CNS**- Central nervous system
- **CWA** – Chemical warfare
- **OP/OPP/OPC**- Organophosphorus compounds
- **PNS**- Peripheral nervous system
- **POP Scale** - Peradeniya Organophosphorus poisoning scale
- **PAM**- Pralidoxime
- **NMJ**-Neuromuscular junction
- **PChE**- Pseudocholinesterase
- **OPIDP**-OP induced delayed polyneuropathy
- **TEPP**-Tetra ethyl pyrophosphate
- **WHO**-World health organisation

CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

OP compound poisoning is an important indication for emergency admission in most hospitals throughout India . OP compounds are used as pesticides, herbicides, chemical warfare agents in form of nerve gases[1,2]. The widespread availability of these compounds has increased the likelihood of poisoning.

WHO estimates that approximately 3 million pesticide poisoning occur worldwide and causing more than 2,20,000 deaths[3]. Developing countries like India report alarming rates of toxicity and death.

OP acts by inhibiting the enzyme cholinesterase, results in accumulation of acetylcholine at synapses and myoneural junction leading to cholinergic over activity[4].

Mortality ranges from 4-30% in Indian studies. Respiratory Failure is the most common complication of OP[5] poisoning leading to death. Early recognition and prompt ventilator support may improve survival. Owing to limited availability of resources, all OP poisoning patients are not managed in IMCUs in Indian setup. It is therefore important that clinical features and criteria to predict the need for ventilator support to be identified at initial examination.

Serum cholinesterase level is depressed after OP poisoning. Peradenya OP compound scale has not been studied much in Indian scenario[6]. It could be a simple and effective system to determine the need for ventilator support early

on in the course. In a study by Senayeke et al, patients with a high score on the POP scale have higher morbidity and mortality[7]. The present study aims to correlate serum cholinesterase level and the clinical criteria score described by the POP scale at initial presentation and the severity of poisoning with need for ventilation.

AIM OF STUDY

To assess the correlation of POP scale and serum cholinesterase level in predicting

1. The clinical severity and outcome of organo phosphorous compound Poisoning
2. To predict the need for ventilatory support , requirement of atropine , and duration of hospital stay

REVIEW OF LITERATURE

HISTORY REGARDING SYNTHESIS OF OP COMPOUNDS:

In 1837, Von Hofmann synthesized methyl phosphor chloride as an OP compound.

In 1848, Voegeli produced the first neutral ester of phosphoric acid, the triethylphosphate (TEP)

In 1854, Clermont produced tetraethylpyrophosphate (TEPP).

TEPP was the first OP cholinesterase inhibitor. TEPP is an effective insecticide, is highly toxic and inactivated by hydrolysis[8].

In 1932, Lange and Krueger reported the cholinergic nervous system effects, choking sensation, and blurred vision following inhalation of dimethyl and diethyl phosphorofluoridates.

In 1934, Dr. Gerhard Schrader, a German chemist, synthesized hundreds of OPs including parathion and tabun (dimethyl phosphoroamidocyanidate), sarin (isopropyl methylphosphonofluoridate), and soman (O-Pinacolyl methylphosphonofluoridate) as CWA.

Tabun and sarin were studied for their use as chemical weapons by Wolfgang Wirth .

Schrader later synthesized a series of fluorine-containing esters including diisopropylfluorophosphate (DFP) and sarin, pyrophosphate esters including TEPP and octamethylpyrophosphortetramide (OMPA), and thio- and thionophosphorus esters including parathion and its oxygen analog paraxon . The potency of some of these chemicals prevented their usage as insecticides, they

were considered to be used as CWA[9,10]. In 1950,the American Cyanamid Company produced Malathion [diethyl (dimethoxyphosphinothioyl) thiobutanedioate]

Now a wide variety of OPs with different biological properties were available and been used as insecticides, nematocides, acaricides, and fungicides. Parathion, malathion, and azinphosmethyl were the first marketed Ops[11].

Organophosphates and carbamates are potent cholinesterase inhibitors capable of causing severe cholinergic toxicity following cutaneous exposure, inhalation, or ingestion. Though structurally distinct organophosphates and carbamates exhibit similar clinical manifestations with toxicity and require similar management following overdose [12].

Medical applications of organophosphates and carbamates :

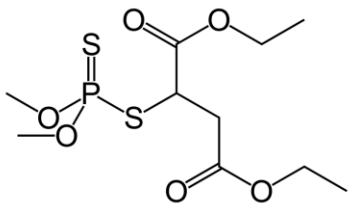
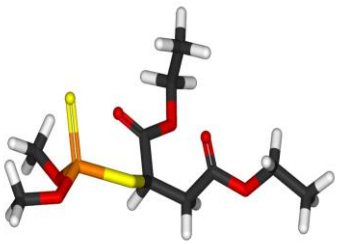
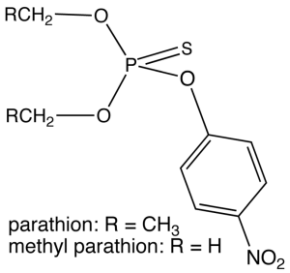
Reversal of neuromuscular blockade:

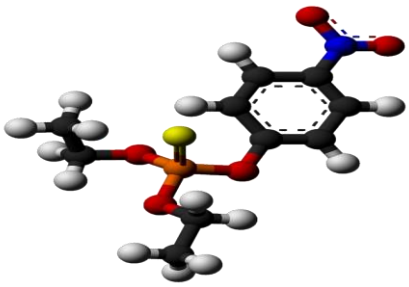
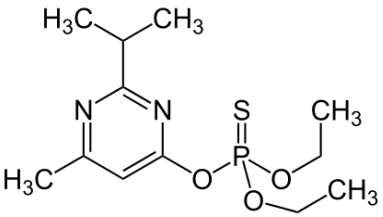
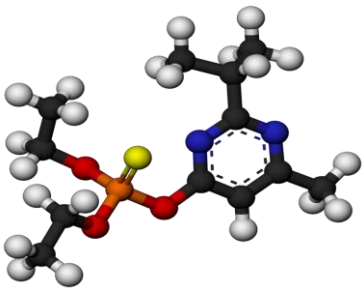
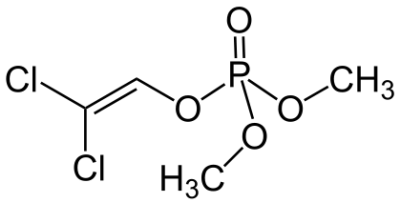
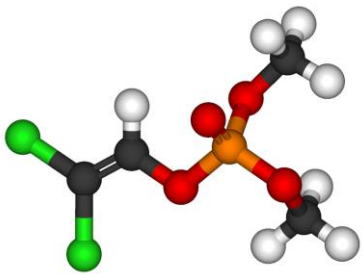
- neostigmine,
- pyridostigmine,
- edrophonium

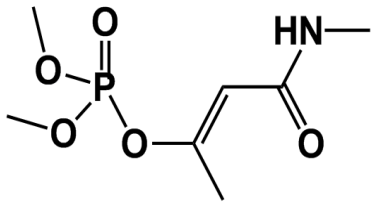
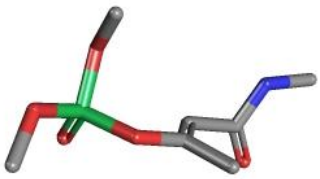
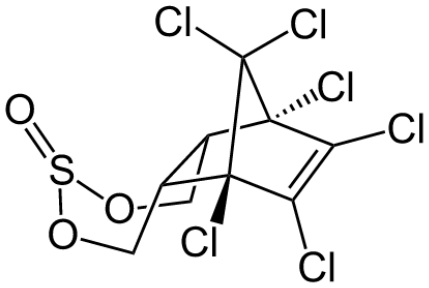
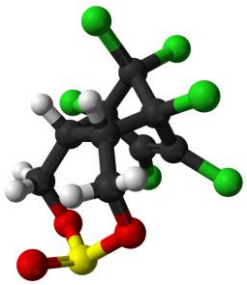
Treatment of glaucoma, myasthenia gravis, and Alzheimer disease:

- echothiophate,
- pyridostigmine,
- tacrine, and
- donepezil [13].

ORGANOPHOSPHORUS POISONING CHEMISTRY :

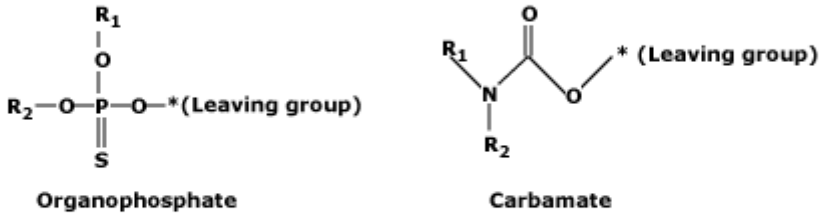
<table>
<tr>
<td>Malathion:
 
  </td>
<td>Parathion
 

  </td>
</tr>
<tr>
<td>Diazinon
 
  </td>
<td>Dichlorvos
 
  </td>
</tr>
</table>

Monocrotophos  	Endosulfan  

STRUCTURAL FEATURES OF ORGANOPHOSPHATES:

General structures of organophosphate (left) and carbamate (right) agents



Organophosphate Carbamate

The variable R1 and R2 groups are composed of either methyl (CH3) or ethyl (CH3CH2) moieties. The leaving group is generally an oxime or an aromatic group. Organophosphorones are similar to organophosphates, but they lack a sulfur atom, and are instead bound to four oxygen molecules.

The basic structure consists of phosphorus, which is bound to oxygen (O) by a double bond, R1and R2may be alkyl, alkoxy, aryloxy, amido, mercaptan or other groups.'X'represents the leaving group, a conjugate base of weak acid is found as a halide, cyanide, thiocyanate, phenoxy, thiocholine or carboxylate group [14].

Organophosphorus compounds inhibit enzyme acetyl cholinesterase. The mechanism of inhibition of the enzyme is by reacting with the esteretic site on the acetyl cholinesterase molecule. The bond formed between phosphorus atom and the esteratic site of enzyme is stable and requires hours to weeks to reverse depending on the type of organophophorus compounds. Phosphorylated enzyme is inhibited because of occupation of its active site. It is not capable of carrying out its normal function of hydrolysing acetyl choline [15].

The effect of organophosphorus compound poisoning is therefore the result of continuing increased production of acetylcholine at the neuromuscular junctions resulting in a depolarization block [16].

The phosphorylated enzyme undergo either spontaneous hydrolysis or dealkylation. Due to spontaneous hydrolysis active enzyme cholinesterase is released and this is called reactivation. The phosphorylated enzyme can also undergo dealkylation. Once this occurs, reactivation is impossible. This process is called 'ageing'[24].

Once ageing occurs recovery of cholinesterase activity depends on synthesis of new enzyme by liver which may take days or weeks.

Hence the three independent reactions determine the speed of onset and severity of poisoning

1. Phosphorylation of cholinesterase by organophosphorus compounds.
2. Reactivation.
3. Ageing.

Organophosphorus compounds are divided into two series of compounds, alkylphosphates (direct inhibitors) like malathion, and arylphosphates (indirect inhibitors) like parathion. Poisoning by direct inhibitors of acetyl cholinesterase presents as an acute cholinergic crisis, they do not develop late type muscular weakness. Response to atropine is rapid.

PHARMACOLOGY:

Broad classification of insecticides: [25]

Organochlorine Compounds	Organophosphorous Compounds	Carbamates
Methoxychlor	Malathion	Carbaryl
DDT	Chlorthion	Propoxur
HCH(BHC) Lindane	Ronnel ,EPN	Dimetilan
Chlordene	Trichlorfos	Pyrolan
Heptochlor	Fenthion	
Dieldrin	Dichlorvos	
Aldrin	Dimethoate	
	Chlorpyrifos	**Synthetic**
	Parathion,	-Pyrethroids
	methyl parathion	
	Diazinon,	
	Dioxathion	

MOST COMMONLY WITNESSED OPC AS POISONING CASES IN EMERGENCY ROOM: [25, 27]

Generic name	Trade name
Endosulphan	Endrin,Jayasulphan
Monocrotophos	Nuvacron, Huvacron
Fenthion	Baytex,Agrocidin,Lebaycid,Fenthiosul
Malathion	Finit, Malatox,agromal
Methyl parathion	Malazene,Sumalathion,Maladan,Kalathion
Metapar	Licel
Phorate	Folidol-M,Agrotex,Parahit,metacid
Methyi Quinalphos	Knockout,Metasystox
Fenitrothion	Tik-20, Folithion, Agrathion, Vikathion,

Less commonly seen OPC as cause of poisoining in hospital [25]

Dimethate, Ethion, Dichlorovas, Phosphomidon, Ediphenphos,

Choloropyriphos, Acephate, Triazphos

Organophosphorous compound classification:[35]

- Older but most commonly used classification:
    - Alkyl phospates
        - TEPP, HETP, OMPA, Malathion, systox ,DFP etc,..
    - Aryl phosphates
        - Parathion, EPN, Chlorothios,Diazinon, Demeton etc,..
- Classification proposed by Holmstedt which is of pharmacological and toxicological interest where compounds are divided into 5 depending on different X in the structure of OP compound.[28]
    - Group A
        - X-halogen, cyanide and thiocyanate
        - SOMAN, SARIN, DFP
    - Group B
        - X-Alkyl, alkoxy, aryloxy
        - DDVP, Forstenon,Pyrazoxon
    - Group C
        - X-Thiol or Thiophosphorous compound
        - Parathion, Malathion, Azethion, Diazinon, Systox and
        - Demeton
    - Group D
        - Pyrophosphates and related compounds

- TEPP, DPDA, OMPA

- Group E
  - Quaternary Ammonium Compound
  - Phospholin

Based on grades of toxicity and use:[29,30]

Highly toxic- Used as agricultural pesticides.

Insecticide	**LD_{50}(mg/kg)**	
	Oral	**Dermal**
1) TEPP	1.1	2.4
2) Mevinphos	3.7	
3) Chlorpyrifos	8	
4) Ethyl parathion	13	21
5) Methyl parathion	14	67
6) Fenthion	15	

Moderately toxic- Used as animal insecticides.

Insecticide	**LD50(mg/kg)**	
	Oral	**Dermal**
1) Leptophos	53	
2) Diohtorvos,DDVP	80	107
3) Trichlorfon	630	>2,000
4) Ronnel	1,250	>4,000
5) Malathion	1,375	>4,444
6) Temophos	2000	>4,000

Low toxicity- Used for field sprays.

Insecticide
1) Diazinon
2) Malathion
3) Dichlorvos

Common causes of OP poisoning;

- Accidental poisoning.
- Self Poisoning.

1. Inhalation: Airborne inhalation of pesticides while applying to plants as well as pets or household surfaces,capets in less ventilated areas.
2. Ingestion: Eating of fruits and vegetables without washing that has treated with pesticides.
3. Drinking water from containers contaminated with discarded poison.
4. Absorption: unwashed hands after handling pesticides.

Pharmacokinectics:

Most organophosphorus compounds are rapidly and well absorbed from the skin, mucous membrane, conjunctiva, gastro-intestinal tract and lungs. These chemicals are detoxified by cytochromeP450 mediated mono-oxygenases in liver. But some metabolites are more toxic than parent compounds as the case in the conversion of parathion, diazinon and malathion to oxons.

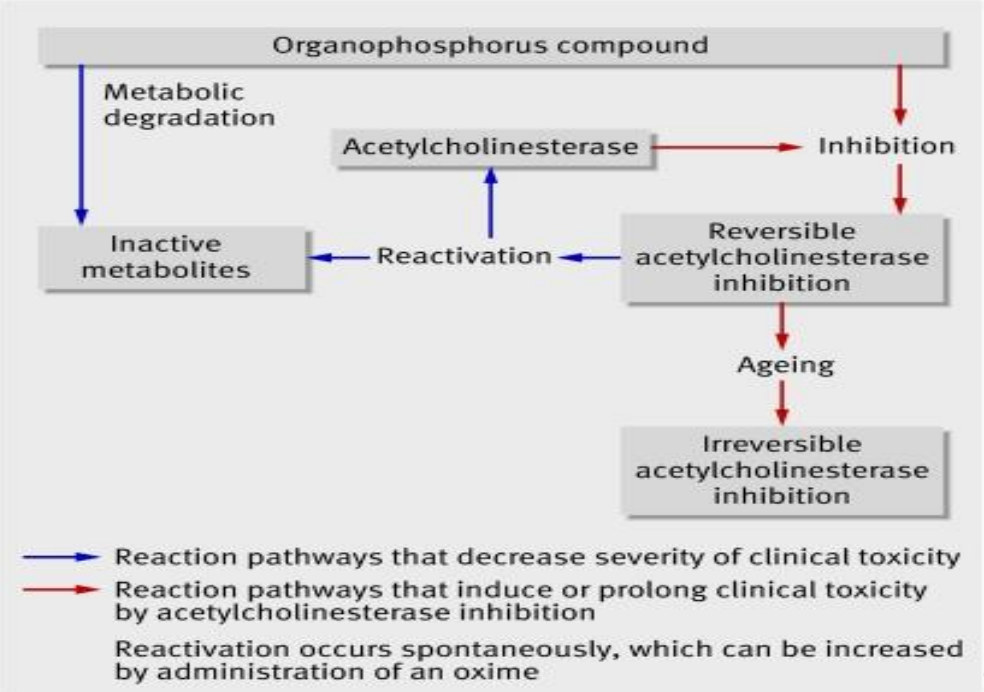
Pharmacodynamics and pathophysiology:

Organophosphates are inhibitors of enzyme cholinesterase. They are esters of carbamic acid or derivatives of phosphoric acid. They firmly or sometimes irreversibly phosphorylate the cholinesterase enzyme .Thus action of

cholinesterase will be inhibited, especially acetyl cholinesterase in synapses and on red-cell membranes, and butyryl cholinesterase in plasma.[31] The breakage of phosphorus-Cholinesterase bond takes 60 minutes to several weeks.[32]

A specific Acetylcholinesterase(true cholinesterase) and a nonspecific Butyrylcholinesterase (pseudocholinesterase) are present in the body.

Features	Acetylcholinesterase	Butyrylcholinesterase
1.Distribution	All cholinergic sites, RBC, grey matter	Plasma, liver, intestine , white matter
2.Hydrolysis Ach	Very fast(micro seconds)	slow
3.Inhibition	sensitive to physostigmine	sensitive to OP
4.Function	Termination of Ach action	Hydrolysis of esters
5.Structure	tetramer	tetramer,342 KD weight
6.half life		12days
7.carbohydrate content	16%	24%



[33]

ANATOMY AND PHYSIOLOGICAL ASPECTS OF ANS:[34]

ANS functions autonomously and also controls the visceral function. It innervates all organs except skeletal muscles .Like somatic nervous system, the ANS consists of afferents, centre and efferents. It controls, sweating, body temperature, gastrointestinal motility and secretion and arterial blood pressure. Anatomically they are divided into sympathetic and parasympathetic components.

Specific features of ANS:

1. It supplies all the organs.
2. The distal most synapse located outside in the ganglia.
3. Preganglionic are myelinated and postganglionic were non- myelinated.
4. It has peripheral plexus formation.
5. The efferent neurotransmitter were Ach, Noradrenaline.

6. There is no denervation atrophy after nerve section in ANS.

Autonomic nervous system centers are located in the hypothalamus, brainstem and spinal cord. It includes

1. **SYMPATHETIC: (thoracolumbar)**
    - Spinal cord - T1 – L1
    - Pre - vertebral ganglia - coeliac and hypogastric
2. **PARASYMPATHETIC: (cranio-sacral)**
    - From central nervous system – III, VIII, IX, X cranial nerves.
    - Spinal cord - S2, S3 and S4 nerves.[35]

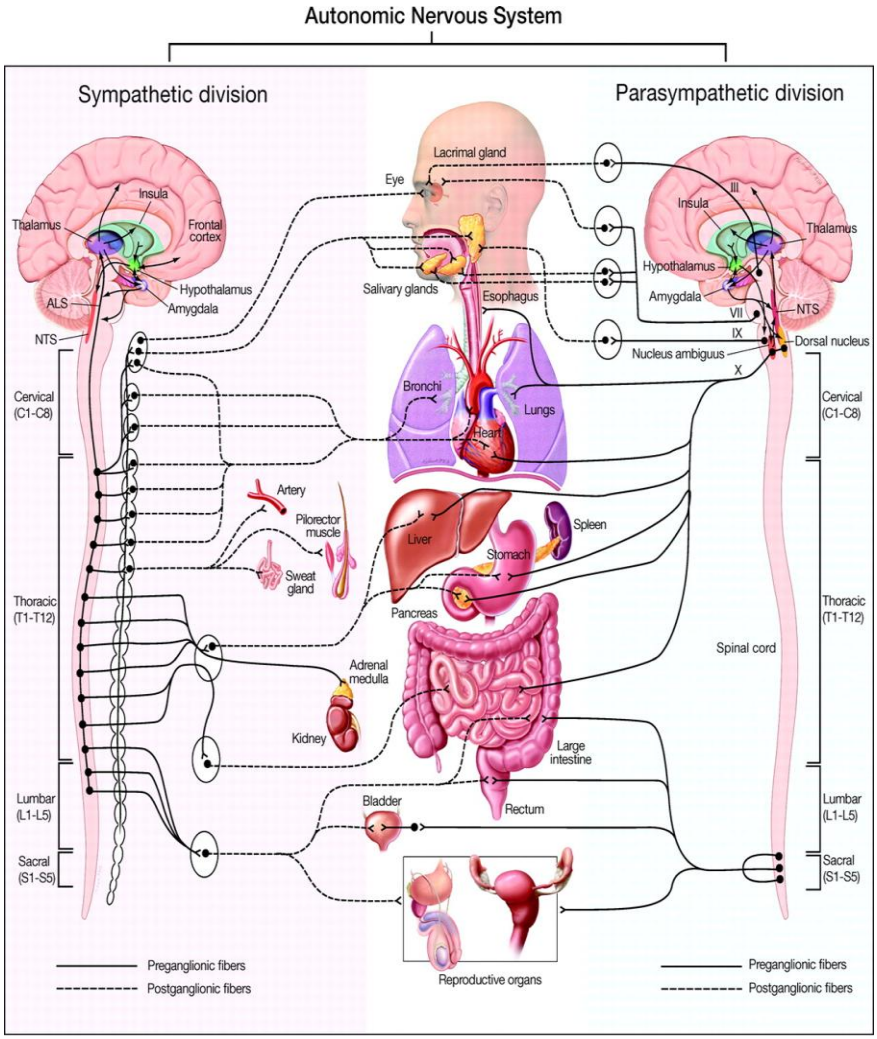
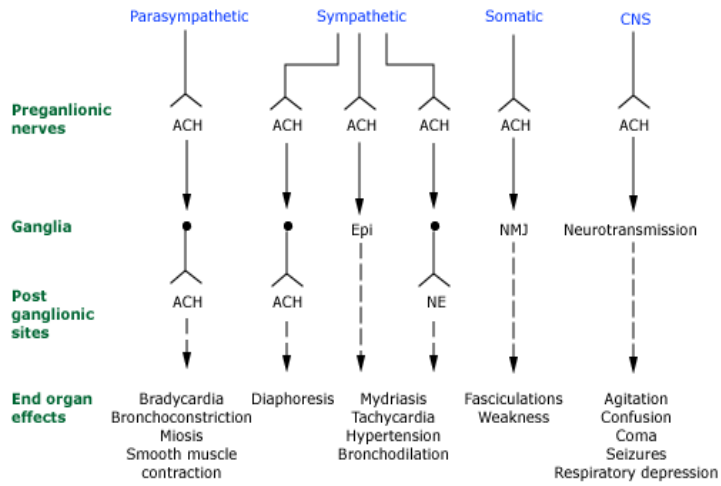


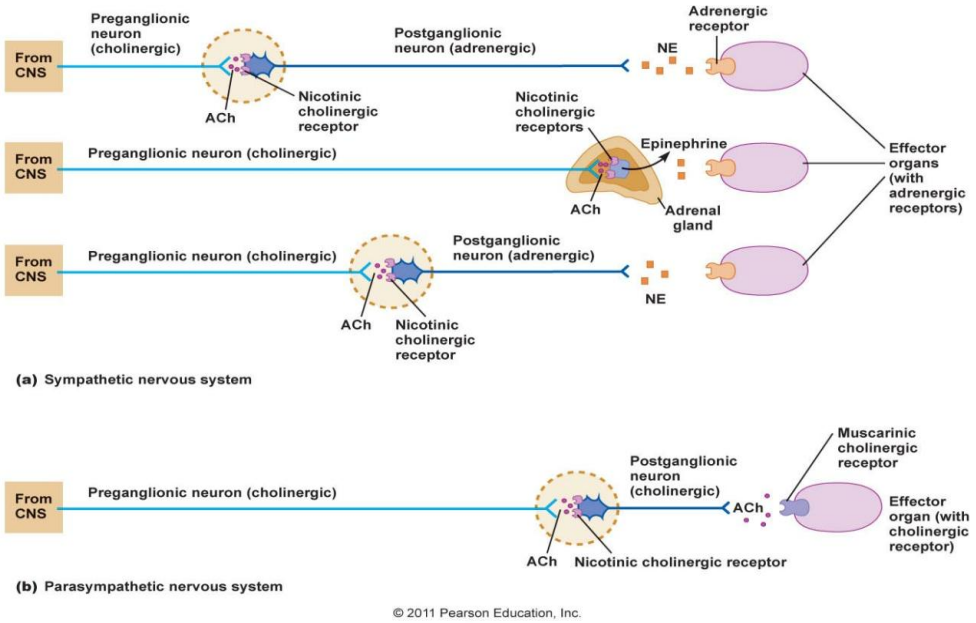
Figure-AUTONOMIC NERVOUS SYSTEM-organ specific arrangement[34]

Neurologic effects of organophosphate and carbamate agents



ACH: acetylcholine; Epi: epinephrine; NE: norepinephrine; NMJ: neuromuscular junction.

Neurotransmitters: [34]



1. Nor-epinephrine (NE) is the neurotransmitter of preganglionic sympathetic neurons and hence they are called as “adrenergic”.
2. At the preganglionic neurotransmission acetylcholine is the neurotransmitter for both divisions of autonomic nervous system as

well as the postganglionic neurons. Hence they are called as "cholinergic" neurons

Cholinoceptors:

Two classes of receptors for Ach are recognised.They are muscarinic and nicotinic,the former is a G protein coupled receptor, while the latter is a ligand gated.

MUSCARINIC RECEPTORS-these are stimulated by muscarine and blocked by atropine.They are located primarily on autonomic effector cells in heart, blood vessels, smooth muscles, eye and glands of respiratory, gastrointestinal and urinary tracts, sweat glands etc,.and in the CNS. subtypes-M_1 to M_5.

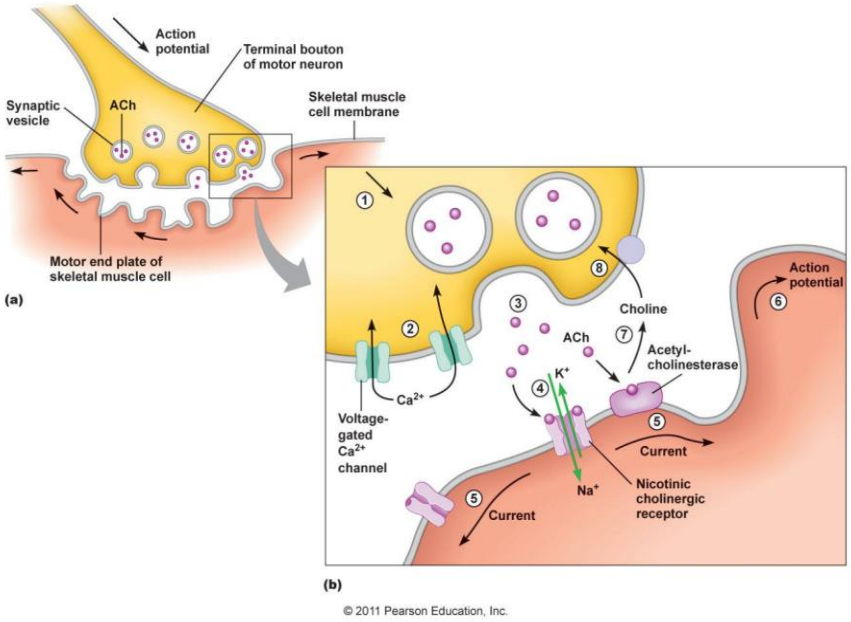
NICOTINIC RECEPTORS-

These are activated by nicotine and blocked by tubocurarine or hexamethonium.

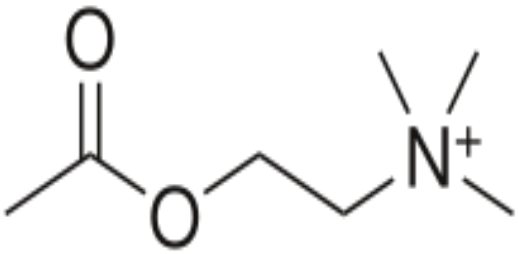
Types-$N_{M,}N_N$

N_M-located at skeletal muscle end plate. They mediate contraction of skeletal muscle. N_N-present on ganglion cells, adrenal medullary cells, brain & spinal cord.

Neuromuscular Junction[34]



ACETYLCHOLINE:



[47]

Acetylcholine (Ach), first synthesized by BAYER in 1867,is a neurotransmitter. It was first recognized as a potent pharmacological substance by HUNT in 1906.[35]

The various stages of acetylcholine formation and release at neuromuscular junction occurs as follows.

1. Golgi apparatus forms small vesicles measuring about 40 nm in the cell body of motor neuron at spinal cord.
2. These vesicles are being transported through the core of the axon from the central body of spinal cord to neuromuscular junction by a method

called “streaming”.The number of vesicles collected at the nerve terminals is about 3,00,000 at single skeletal muscle end plate.

Acetylcholine is synthesized in the cytosol of the terminal nerve fibers and then transported through membranes of the vesicles to their interior, where it is stored in highly concentrated form with about 10,000 molecules of acetyl choline in each vesicle.

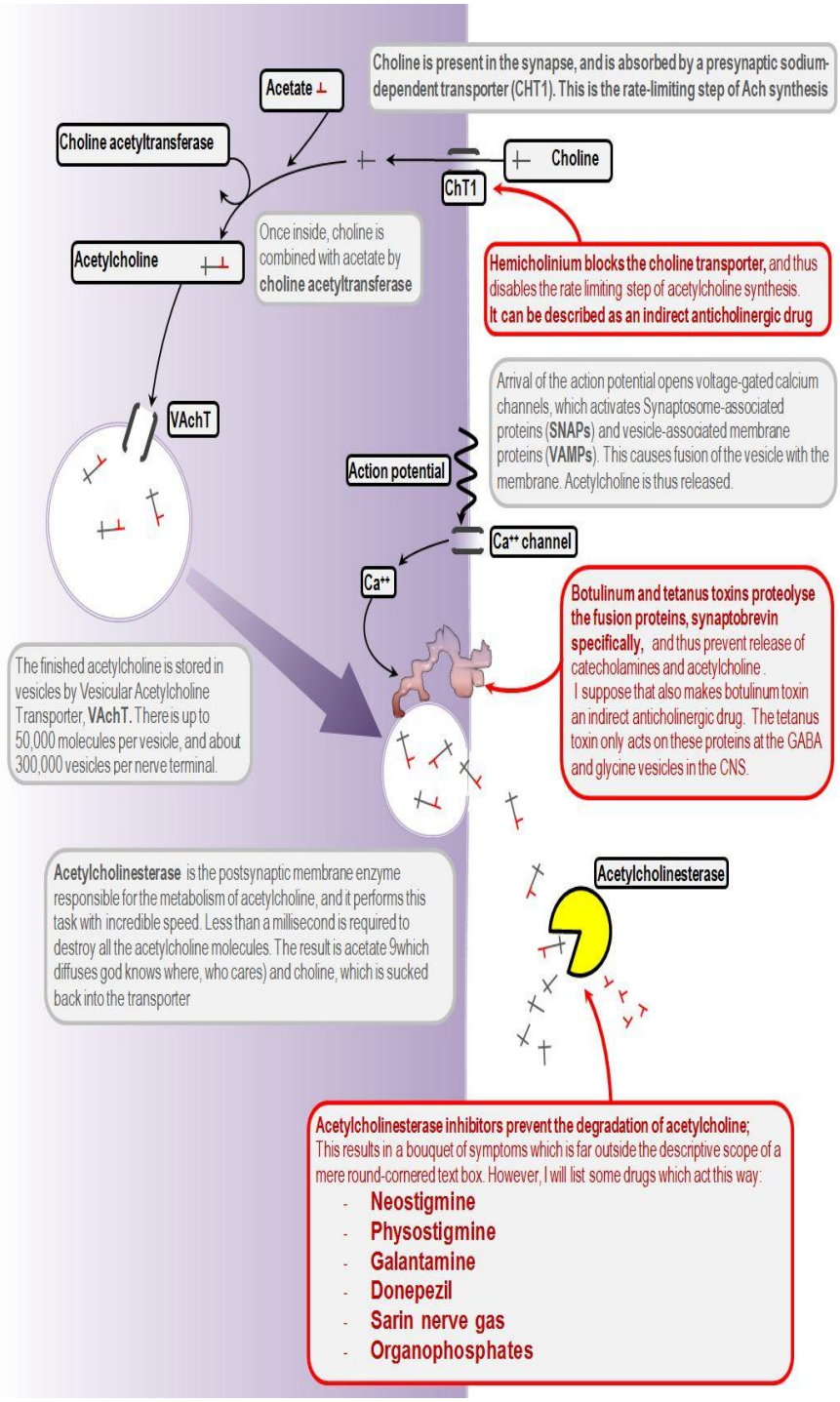
SYNTHESIS ,STORAGE AND RELEASE OF ACETYLCHOLINE

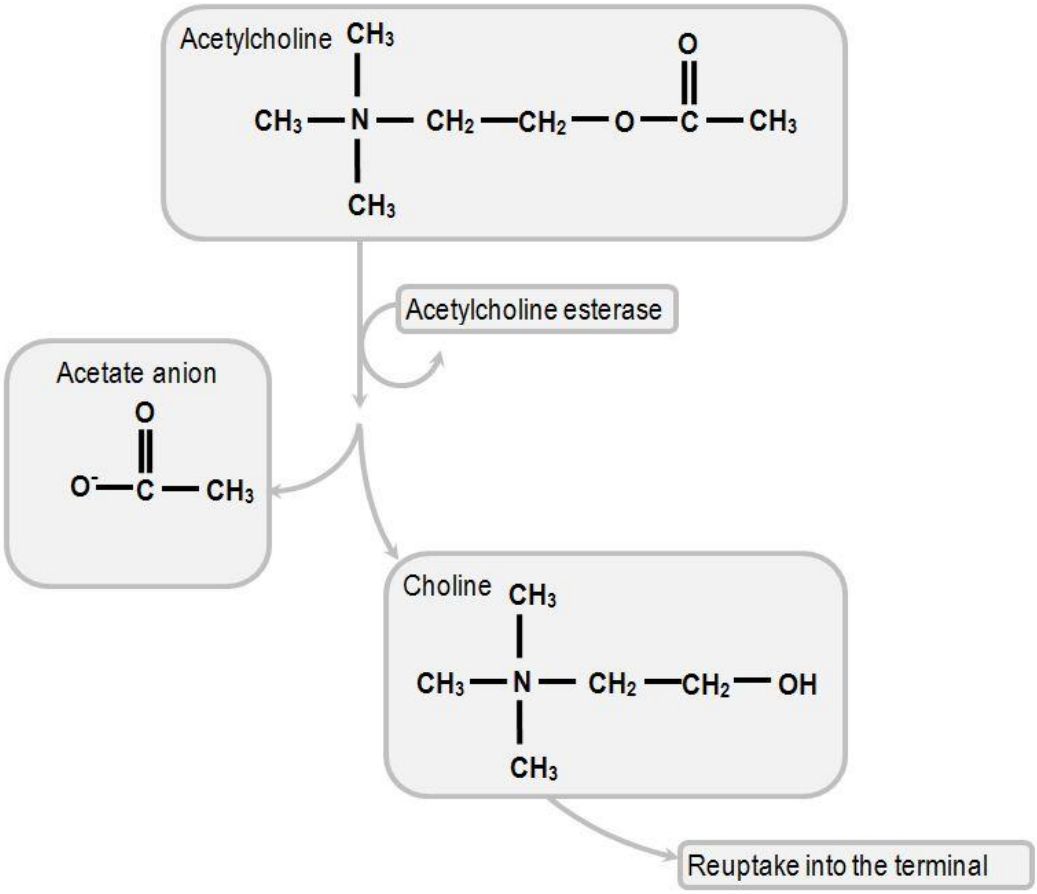
[37,38,39].

When an nerve impulse arrives at the nerve terminal, it opens many calcium channels in the membrane at the nerve terminal causing release of acetyl choline into the synaptic space. On an average 125 vesicles are ruptured with each action potential.

Duration of acetylcholine is curtailed since it is hydrolysed by the enzyme acetylcholinesterase, which is bound in collagen and glycosaminoglycans in the local connective tissue. The choline is reabsorbed actively into the neural terminal to be reused in forming new acetylcholine.

The Ach in the motor nerve terminal is synthesized in the axoplasm





Once its function in the synapse is over, synaptic acetylcholine esterase breaks it back down into acetate anions and choline. This hydrolysis takes less than a millisecond.

The acetate goes presumably back into Krebs cycle and the choline is reabsorbed by its uptake (one Na+ /Cl- dependent high affinity transporter and another independent transporter of lower affinity).This reuptake is the rate-limiting step in acetylcholine synthesis[37,38,39].

ACETYLCHOLINESTERASE(AChE) :

History of Acetylcholinesterase(AChE):

In 1968 , Walo Leuzinger et al from Columbia University, NY first purified and crystallised acetylcholinesterase

Acetylcholinesterase is present in three forms in human body:

Brain acetylcholinesterse:

Brain acetylcholinesterase is like RBC esterase. In brain it is seen as tetramer (G4 form) as well as monomer (G1 form).

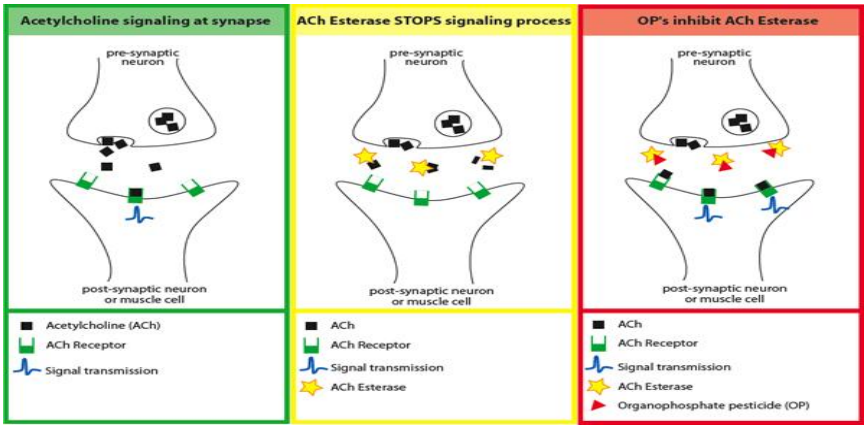
CAUSES OF CHOLINESTERASE LEVEL ABNORMALITIES:

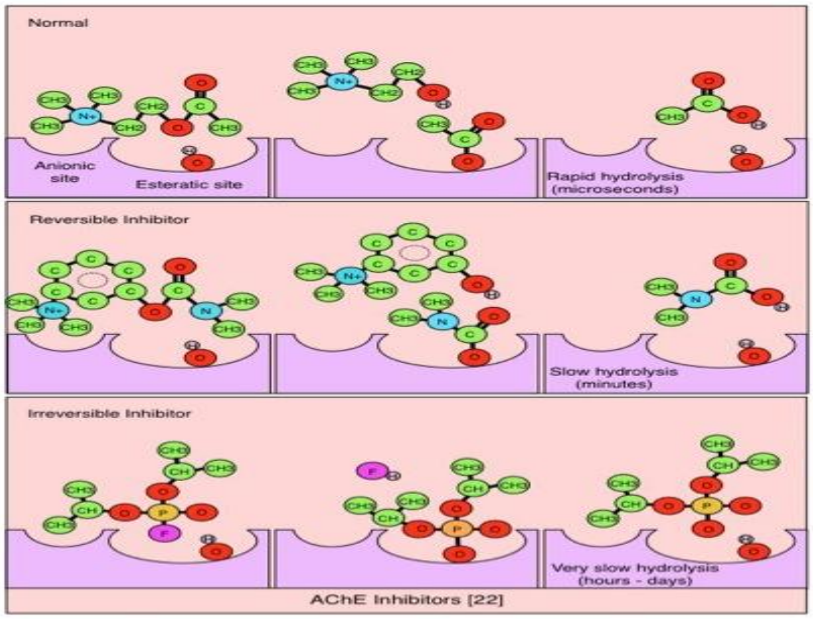
Abnormalities	RBC Cholinesterase	SERUM Cholinesterase
Low level	1.antimalarial drugs 2.oral contraceptives 3.anemias mainly pernicious anemia	1.acute infections 2.benzalkonium salts 3.carbon disulphide 4.chronic disease 5.codeine,cocaine 6.dermatomyositis 7.morphine,malnutrition 8.pregnancy,pills

- **RBC acetylcholinesterase**
  - specific or true acetylcholinesterase
  - Red cell, nervous tissue, skeletal muscle.
- **Plasma acetylcholinesterase**
  - butryl or Pseudo cholinesterase
  - Plasma, liver, heart, pancreas, brain

Acetyl cholinesterase is a protein attached to the basement membrane of the muscle and membranes of the motor end plates and the nerve terminals. Each molecule of the enzyme is able to bind and hydrolyze several molecules of acetylcholine.

Organophosphate attacks Acetylcholinesterase:



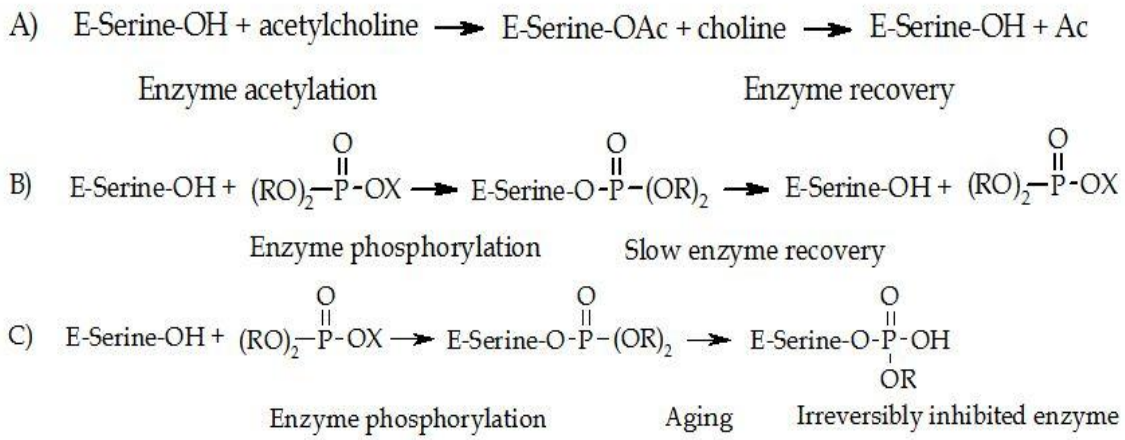


The biological effects of OP compounds are due to accumulation of endogenous acetyl choline at sites of cholinergic transmission. Ion binding is by which enzyme AChE is inhibited, but eventually progressively phosphorylated by covalent bonding a process normally takes 24-48 hrs. This process is called “Ageing” and this period is known as the “critical interval”

because during this time administration of antidote is still effective in reversing the process. Once ageing is completed the enzyme cannot be reactivated.

Plasma AChE recovers quickly within 4 weeks. Red cell AChE takes longer and may not be restored. Affected AChE recovers at the rate of 1% per day. Restoration of AChE activity occurs by slow denovo synthesis of free enzyme and also to some extent as a result of spontaneous dephosphorylation of the inhibited enzyme.

The inactivation (phosphorylation) and reactivation (dephosphorylation) vary considerably with different OP compounds, which accounts for differences in toxicity. Ageing has an important bearing on toxicity and treatment outcome. Oximes cannot reactivate aged phosphorylated enzyme.



CHANGES IN ACETYLCHOLINESTERASE LEVELS DURING POISONING AND TREATMENT :

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

- Cholinesterase activity of red blood cells is instantly and completely restored and long lasting, but the return of activity of serum cholinesterase (SChE) is transient and variable after oximes. (The main effect produced by the administration of oximes is the restoration of the true acetylcholinesterase activity & prompt and complete relief of symptoms, especially after alkylphosphate poisoning). True cholinesterase level indicates effectiveness and serum cholinesterase levels indicate the prior presence of cholinesterase inhibitor.[41,42]

- Time of ingestion & relation to serum cholinesterase activity : A definite correlation between time of ingestion and serum cholinesterase activity is found viz., longer the interval lower the activity. It appears that in doubtful cases or in cases with bizarre clinical picture, and in cases where more than one poisonous substance is ingested, the estimation of

serum cholinesterase activity would be of some importance in the diagnosis of the case.

In patients with liver disease not only do they have decreased levels but a further decrease ensues as a result of exposure to an organophosphorus compound. Serum cholinesterase is sharply reduced in acute myocardial infarction and below normal in dermatomyositis. Nephrotic syndrome patients have increased levels of serum cholinesterase.

DISADVANTAGES OF SERUM CHOLINESTERASE ESTIMATION

Following pralidoxime administration, true cholinesterase levels indicate the effectiveness of PAM and serum cholinesterase levels indicates prior presence of cholinesterase inhibition even after recovery of true cholinesterase activity by PAM, hence the latter cannot be used to assess the effectiveness of PAM therapy.

- Serum cholinesterase level at a particular time in the blood is not constant but continuously changing as the inhibition of the enzyme by inhibitors and spontaneous reactivation will take place simultaneously.

CLINICAL FEATURES:

The signs and symptoms of cholinesterase poisoning can be classified into three categories

1. Muscarinic: Postganglionic parasympathetic manifestations
2. Nicotinic: Autonomic ganglionic and somatic motor (neuromuscular junction) effects
3. Central: Central nervous system effects

MUSCARINIC SYMPTOMS:

SWEAT GLANDS	excessive sweating
PUPILS	Contricted
LACRIMAL GLANDS	Lacrimation, chromolachryorrhea
SALIVARY GLANDS	excessive salivation
BRONCHIAL TREE	wheezing, crackles, pulmonary edema
GIT	cramps, vomiting, diarrhea, tenesmus
CVS	bradycardia, hypotension
CILIARY BODY	blurred vision
BLADDER	urinary incontinence

NICOTINIC SYMPTOMS:

STRIATED MUSCLE	fasciculations, cramps, weakness, twitching,
SYMPATHETIC GANGLIA	Hypertension, Tachycardia

CNS EFFECTS:

Giddiness, tension, anxiety, restlessness, emotional lability, excessive dreaming, insomnia, headache, tremor, depression, drowsiness, confusion, slurred speech, generalized weakness, coma with absence of reflexes , type I paralysis, abnormal breathing pattern , seizures, depression of respiratory and circulatory centres with dyspnoea, cyanosis and fall in blood pressure.

- Immediate onset -Acute cholinergic syndrome
- Intermediate Syndrome is characterised by Delayed respiratory failure(24-96hrs)
- OPC induced delayed peripheral neuropathy.

OTHER FEATURES:

Acute organophosphorus poisoning is characterized by the following clinical features depending upon receptors involved like;

ACUTE CHOLINERGIC SYNDROME (Acute muscarinic syndrome / Wadia Type I syndrome) :

Usually lasts 24-48 hours. Its manifestations include;

Ophthalmologic :

Miosis, lacrimation, and blurred or dim vision

Cardiovascular :

Bradycardia , Hypotension (cardiac muscarinic (M2) receptors).

Tachycardia , hypertension (nicotinic).

Dysrhythmias and conduction defects

QT prolongation and ST, T wave anomalies (severe poisonings)

Respiratory:[43]

A. Bronchial hypersecretion and wheezing (muscarinic)

B. Muscle weakness or paralysis of the respiratory center (nicotinic)

C. Non-cardiogenic pulmonary edema (severe exposure).

Neurologic :

Headache, seizures, respiratory depression, coma, mental status changes, fatigue, lethargy, agitation, depression, hallucinations, slurred speech, ataxia and extra pyramidal manifestations (CNS muscarinic GABA-nergic antagonism particularly in limbic and cortical structures).[44]

Gastrointestinal:[45]

Excessive salivation. Gastrointestinal smooth muscle contractions resulting in nausea, vomiting, diarrhea, faecal incontinence and intestinal cramping (muscarinic).

Genitourinary :

Urinary incontinence (muscarinic)

Hematologic : Inhibition of acetylcholinesterase.

Dermatologic :

Sweating (muscarinic)

Immunity:

Parathion suppresses both IgM and IgG. Elicit autoimmune reactions and impair natural killer cell and cytotoxic T-cell function.

Musculoskeletal :

Skeletal muscle fasciculations and twitching, weakness, and paralysis (nicotinic)

Metabolic and endocrine :

An increase of plasma corticosterone, TSH concentration, nonketotic hyperglycemia and glycosuria.[46] Hyperamylasemia occurred in 47% of patients poisoned with malathion.[47]

Teratogenicity:

Pre and postnatal death and congenital abnormalities like vertebral, limb abnormalities, cleft palate, polydactyly and hydroureter.[48]

Vocal cord paralysis:

Progressive respiratory distress and stridor.

Temperature regulation:

Hypothermia (muscle paralysis and excessive diaphoresis)

INTERMEDIATE SYNDROME :

In 1974, Wadia et al first termed as type II paralysis, is a syndrome characterized by muscle paralysis following the acute cholinergic phase. The terminology was later changed by Senanayake and Karalliedde in 1987 to Intermediate syndrome due to the fact that it arises between the period of early cholinergic syndrome and the late onset peripheral neuropathy. The interme diate syndrome which occurs 24 to 96 hours after acute cholinergic crisis is characterized by the following clinical features like inability to lift the neck and sit or stand up, weakness in motor cranial nerves, proximal muscle weakness, areflexia and respiratory paralysis with occasional dystonic posturing.[49]

CAUSES*:* Neuromuscular transmission defect,toxin induced muscular instability,inadequate treatment of acute phase.

DELAYED POLYNEUROPATHY :

Delayed polyneuropathy usually sets in 7-14 days after exposure to an organophosphorus agent results in disability due to symmetrical peripheral muscle weakness. The sensory component if present is milder than the motor component.[44]

The mixed sensory-motor neuropathy usually begins in the legs, causing burning or tingling, then weakness and ataxia. Severe cases progress to

complete paralysis, impaired respiration and death. The nerve damage of organophosphate-induced delayed neuropathy is frequently permanent. Mechanism appears to involve phosphorylation of esterases in peripheral nervous tissue and results in a "dying back" pattern of axonal degeneration. Recovery requires weeks to months, and may never be complete. There seems to be no relationship between the severity of acute cholinergic effects and delayed neurotoxicity.

MUSCARINIC FEATURES (WADIA TYPE 1 SYNDROME)	NICOTINIC FEATURES- WADIA TYPE 2 SYNDROME	CNS FEATURES- LESS WITH CARBAMATES
Miosis	Muscle fasciculations (striated)	Unconsciousness
Sweating / Diaphoresis	Paralysis	Confusion, fatigue
Bronchorrhea / Bronchospasm	Muscle weakness	Toxic psychosis, seizures
Bradycardia	Hypertension	Respiratory depression
Hypotension	Tachycardia	Ataxia, dysarthria
Vomiting		Extra pyramidal features
Diarrhea		
Salivation		
Lacrimation		

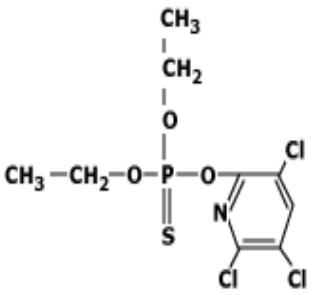
OTHER MANIFESTATIONS :

Other manifestations of organophosphorus poisoning include the following;

1. Landry -Guillian-Barry syndrome
2. Delayed neurotoxicity, which appears 8-12 days following exposure and lasts for weeks and months.
3. Hyperamylasaemia and acute pancreatitis have been reported after oral or dermal exposure in man.[50]

Agents associated with organophosphorous induced delayed neuropathy

Chlorpyrifos
Leptophos
Malathion
Merphos
Mipafox
Trichlorfon
Triorthocresylphosphate (TOCP)



Chlorpyrifos

DIFFERENCE BETWEEN INTERMEDIATE SYNDROME AND DELAYED POLYNEUROPATHY:

	Intermediate syndrome	Delayed Polyneuropathy
Latent period	1-4 days	2-3 weeks
Site of weakness	Proximal	Distal
Limb muscle	Involved	Not involved
Neck muscle	Involved	Not involved
Cranial Nerve	Yes	No
Respiratory muscle	Involved	Not involved
Electromyogram	Tetanic fade	Denervation

REBOUND PHENOMENON

Patients who apparently recover in terms of level of consciousness and pulmonary oedema fall back into a terminal phase. This has been attributed to toxic myocarditis and intestinal reabsorption of organophosphorus compounds .Compounds can remain bound to fat or adipose tissue for a long time and their sudden release result in rebound phenomenon.

The cause of release is:

1. The continuing absorption of the toxin after the transient effect of oximes has subsided and
2. Early reduction in atropine dosage when serum cholinesterase depression is still present.

DIAGNOSIS OF ORGANOPHOSPHORUS POISONING:

- ❖ History of poisoning
- ❖ Smell of poisoning
- ❖ Then look for muscarinic symptoms of poisoning[30]
- ❖ Improvement of signs and symptoms on use of atropine and pralidoxime.
- ❖ Measurement of cholinesterase activity in the blood[58]
- ✓ Take blood samples for the estimation of cholinesterase enzymes
- ✓ Measure the cholinesterase enzyme level whether increased or decreased
- ✓ Decrease in cholinesterase level is indicative of OP poisoning

OPC poisoning is diagnosed clinically and its important to diagnose as early as the patient is admitted to begin the treatment to prevent complications and death as OPC poisoning is associated with high mortality.

Patients are categorised to have mild, moderate or severe poisoning depending on symptoms, signs, cholinesterase levels for management purposes in terms of preventing complications and to improve prognosis .Many studies and many authors have given many gradings and few of important ones are as follows:

DETERMINATION OF SEVERITY OF OP POISONING :

- According to cholinesterase levels[53] given by Proudfoot and symptomatology, normal serum acetyl-cholinesterase / RBC Cholinesterase level is 4500-12500 U/L.

Mild	Moderate	Severe
Walks and talks headache, dizzy nausea, Vomiting Abdominal pain Sweating, salivation Rhinorrhoea	Cannot walk Soft voice muscle twitching (fasciculations) Anxiety, restlessness Small pupils (miosis	Unconscious, no papillary reflex. Muscle twitching, flaccid paralysis. Increased bronchial secretions. Dyspnoea crackles / wheeze. Possible convulsions Respiratory failure
serum AChE 20-50% of normal	serum AChE 10-20% of normal	serum AChE <10% of normal

Dreisbach grading[54]

Mild	Moderate	Severe
Anorexia Headache Dizziness Weakness Anxiety Tremors Impaired vision	Nausea Salivation Lacrimation Abdominal cramps Vomiting Sweating Bradycardia Fasciculations	Diarrhoea Pinpoint pupil Respiratory distress Pulmonary oedema Cyanosis Sphincter disturbances Convulsions Coma Heart block

Grading of toxicity according to Balani[55]

GRADE I	GRADE II	GRADE III	GRADE IV	GRADE V
No symptoms and signs	Vomiting Diarrhoea Abdominal pain and giddiness	miosis with or with-out above symptoms	pulmonary edema with or without any finding of grade 2 and grade 3	Unconsciosness with miosis and with or without presentation of grade 3 and Grade4

According to Patel et al[56]

Signs and symptoms	**Points**
Nausea,vomiting,diarrhea, Sweating	1
Lacrimation,salivation,miosis, Fasciculations	2
Seizures, incontinence, apnea, Areflexia	3
ARDS, proximal muscle weakness	4
Coma	5
Respiratory paralysis	8

Points	Grade
<6	Mild
7-10	Moderate
11-16	Moderately Severe
>16	Severe

Recently Senanayake N. proposed POP scale for grading the severity

Paradeniya Organophosphorus Poisoning scale(POP)[57]

PARAMETER	SCORE
MIOSIS	
Pupil size > 2mm	0
≤ 2mm	1
Pinpoint	2
FASCICULATIONS	
None	0
Present but not generalized	1
Generalized and continuous with central cyanosis	2
RESPIRATION	
RR ≤ 20/min	0
RR > 20/min	1
RR > 20/min with central cyanosis	2
BRADYCARDIA	
PR > 60/min	0
PR 41-60/min	1
PR ≤ 40/min	2
LEVEL OF CONSCIOUSNESS	
Conscious and rational Im-	0
paired, and responds to oral commands	1
Impaired and no response to oral com-	2
mands(if fits present add 1)	
Total	**11**

Score	Grade
<4	Mild
4-7	Moderate
>7	Severe

The patients with grade 3 manifestations on day 0 of admission have high risk of respiratory failure hence increased need for mechanical ventilator and also emergence of other complications and increased stay in ICU is observed.

Grading of Fasciculation

Grading done by giving 1 point each to anterior chest, posterior chest, anterior abdomen, posterior abdomen, right arm , left arm, right thigh, left thigh, right leg and left leg.

MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING: [58,59]

The treatment of a patient of suspected OPC Poisoning is initiated even before his/her admission to casualty in terms of decontamination by washing the contact body surface, removal of clothes and at arrival to casualty with suspicion of OP poisoning, history, examination, and specific treatment with investigations are carried out concurrently to reduce morbidity and mortality associated with OP poisoning The standard treatment of the OP poisoning includes

- **Specific Therapy:**

Three types of drugs are used for OPC intoxication :

1. An anticholinergic , to neutralise the effects of ACh overaction at cholinergic receptors→ATROPINE

   - ✓ Most commonly used physiological antidote acts as competitive antagonist at synapses,
   - ✓ It is an alkaloid derived from a plant Atropa belladona and Datura stramonium poisoning.
   - ✓ Atropine is partially detoxified in the liver and partly excreted unchanged in the kidney and
   - ✓ Adverse effects are: Dry mouth, hot dry skin, thirst, flushing, fixed dilated pupil, tachycardia, impaired speech, tremor, coma, convulsions, respiratory failure and collapse.

2. CNS depressor, which acts as an anticonvulsive → DIAZEPAM and

3. An oxime to reactivate inhibited AChE → PRALIDOXIME.

The treatment of OP poisoning described by Petroianu[59] is AFLOP.

A = Atropine,
FL = Fluid,
O = Oxygen,
P = Pralidoxime (oxime)} along with

- ❖ **Supporting measures,** which include
  - o Oral suctioning of secretions .
  - o Airway protection and ventilation.
  - o Maintenance of circulation
- ❖ **Prevention of absorption:**

- Decontamination
  - Skin decontamination and
  - GI decontamination by
    - Gastric lavage
    - Induced emesis,
    - Use of adsorbant –Activated charcoal,
    - Use of Cathartics and
    - Bowel wash.

❖ **Enhanced elimination.**

- Because of the large volume of distribution of OPC, the dialysis is not indicated[60]

❖ **Prevention of complications and its management.**

OBJECTIVES OF TREATMENT

- Removal and Reduction of absorption of the toxin
- Increase elimination
- Toxin neutralization.

Reduction of further Absorption

- Removal from surface of skin, eyes and hair
- Gastric lavage
- Activated charcoal administration and cathartics
- Bowel irrigation

- Decontamination of skin :
    - Removal of the contaminated clothes
    - Washing with soap and water[76] .

Gastric Decontamination

- Gastric lavage
- Activated charcoal 25 g 2 hourly
- Sorbitol as cathartic.

Gastric Lavage

- Done on CONSCIOUS patients
- Absorption is decreased by 42% if done at 20 minutes and by 16% if done at 60 minutes
- The stomach is first aspirated and then repetedly instilling and aspirating fluid
- Left lateral position is prefered
- Tap water: 5–10 mL/kg is used for lavaging

Treatment:

Anticholinergic Agents

- Atropine or glycopyrrolate

Atropinization targets:

- Systolic blood pressure greater than 90 mm Hg
- Heart rate around 110/minute
- Lung fields are clear.
- Pupils mid position
- Bowel sounds present
- On Day 2: Heart Rate greater than 100/minute
- On Day 3: Heart Rate greater than 90/minute
- On the Subsequent days the heart rate is maintained [77] around 80/minute.

Atropine Dosage

- Recommendations > 20 mg atropine
- 0.02–0.08 mg/kg

Anticholinergic Dose

- 1–2 mg initial bolus dose
- Double dose every 5 minutes if targets not met
- In 20 minutes can achieve atropinization for a dose of 25 mg.

Atropine

The mainstay of treatment of acute OP poisoning

Atropine is an antagonist to receptors of acetylcholine .

Reverses the cholinergic effects of organophosphate poisoning like decreased heart rate, increased bronchial secretions, urination, lacrimation, etc.

Atropinization can be given in two ways

(1) bolus dose administration

(2) incremental dose administration with rapid escalation.

The aim of treatment is to prevent bradycardia, maintain blood pressure, clear lungs and dry skin.The toxic effects of atropine are tachycardia, atropine psychoses and agitation . CNS penetration with glycopyrolate is less and with less CNS toxicity[78.]

The incremental dosage regimen of atropine is superior to bolus dose administration.

Incremental dose : 1.8–3 mg atropine by intravenous (IV) infusion,

repeating the dose every 5 minutes interval

doubling the dose each time till atropinization occurs,

followed by 10–20% of atropine required for atropinization, every hour by IV infusion.

Bolus dose: 2–5 mg of atropine every 10–15 minutes followed by maintenance after atropinisation.

The incremental dosage have a better outcomes of survival and intermediate syndrome. Routine usage of glycopyrolate alone or in combination with atropine usage is not clear[79].

ROLE OF OXIMES IN OP POISONING :

- Reactivate acetylcholinesterase
- They are Nucleophilic agents

- Older compound is pralidoxime
- Newer compounds are obidoxime and trimedoxime .

Toxicity of OXIMES:

- Muscle weakness
- Dizziness, flushing, numbness can be caused by rapid infusion
- High anti-cholinesterase activity can lead to formation of stable phosphoryl oximes

DOSAGE: 30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/hour infusion [80]

INDICATIONS FOR VENTILATORY SUPPORT:

I. Respiratory Gas Tensions

i Direct Indices

Arterial Oxygen Tension < 50 mm Hg on room air

Arterial Co_2 Tension > 50 mm Hg in the absence of metabolic alkalosis

ii Derived Indices

P a o_2/ Fio_2 < 250 mm of Hg

PA-aOo_2 (Pulmonary arterial-alveolar O2 gradient) > 350 mm of Hg

Vd/Vt> 0.6

II. Clinical - Respiratory Rate (RR)> 35 breaths/min

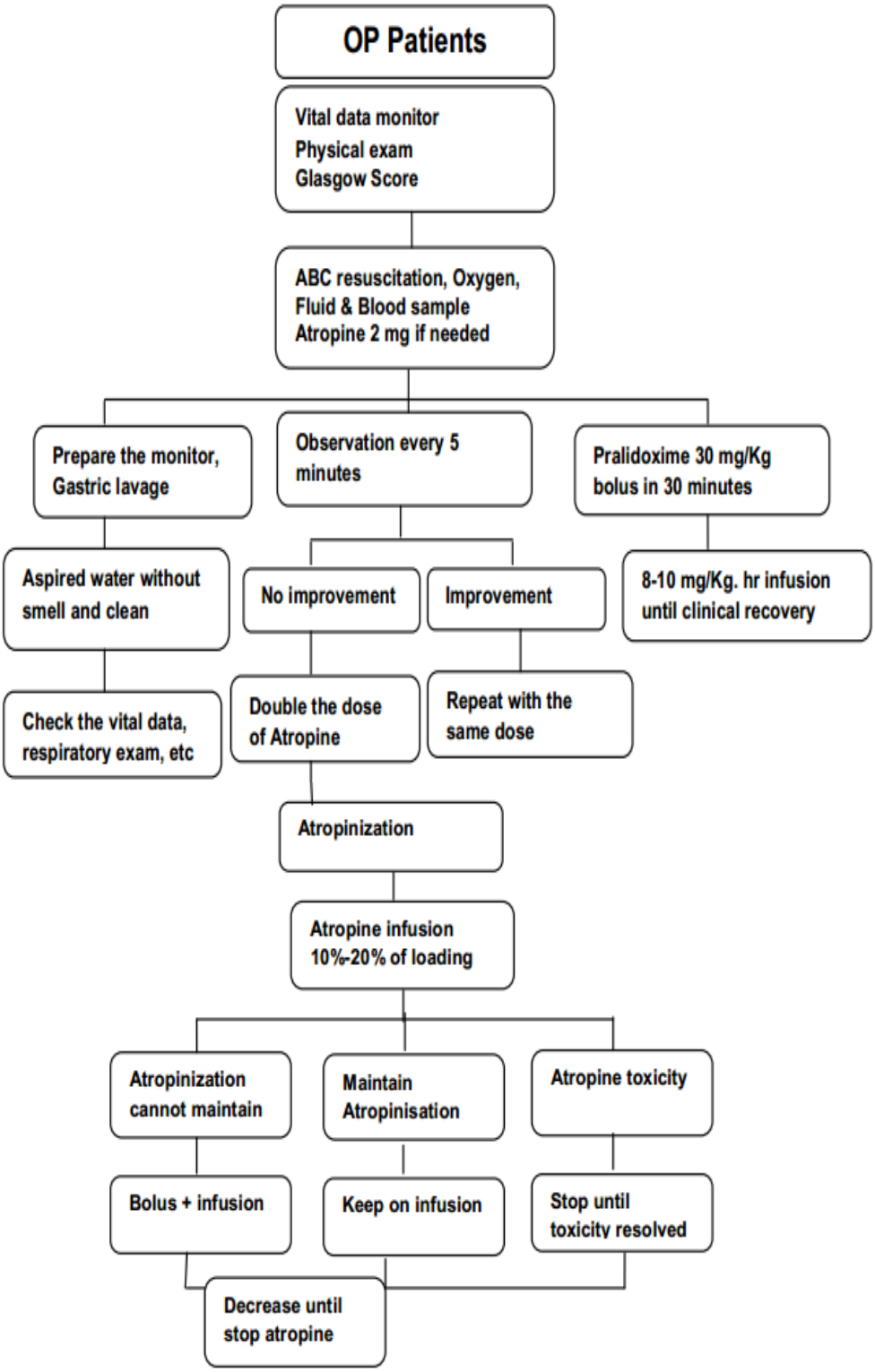
III. Mechanical Indices

Tidal Volume 5 ml/kg

Vital capacity < 15 ml/kg

Maximum inspiratory force <- 25 cm of H_2O

TREATMENT PROTOCOL



Observation of patient of OP poisoning:

It is very important to keep the patient in close observation for minimum three days to two weeks to verify that symptoms of OP Poisoning like muscarinic effects do not recur when atropine is withdrawn.

EXPERIMENTAL THERAPY[74]:

1. Benzodiazepines -these are useful adjuncts to atropine. They increased survival and decreased the incidence of associated neuropathies[72]
2. Sodium bicarbonate: alkalinisation of the serum to pH 7.5 may be useful as hydrolysis of the esteretic portion of the organophosphorus molecule[72]
3. Adenosine receptor agonists
4. Glutamate-receptor antagonists: e.g. felbamate and selective NMDA-receptor channel blockers such as dizocilpone and procyclidine.
5. Clonidine : blocks acetylcholine release but also causes transient inhibition of acetyl cholinesterase.
6. Haemoperfusion[73]
7. Annealed erythrocytes : can constantly remove organophosphorus compound that is being slowly released in to the blood stream from fatty tissues.
8. HI-6 :An alternative oxime, has excellent acetyl cholinesterase regenerating action.
    a. HI-6 is three to five times more effective than 2 PAM[75].

b. HI-6 has been administered as a single intramuscular injection of 500 mg, administered 4 times daily for a maximum of 7 days, in conjunction with atropine and diazepam therapy, for organophosphate pesticide poisoning.

9. Pyridostigmine: It is an inhibitor of acetylcholinesterase and protects the enzyme against inhibitory effects of nerve agents.
10. Trimedoxime
11. ATPase and inhibitory effect on acetylcholine release.

1. Magnesium sulphate

Mechanism of action: It decreases the release of Ach from presynaptic ends by blocking the ligand gated calcium channel.

- Prevents the overstimulation central nervous system buy activation NMDA receptor.

This may reduce OP-induced QT interval prolongation and ventricular tachycardia. Beneficial effects of magnesium have been shown in a small study where magnesium sulphate was administered in a dose of 4 g over 24 h.

14. Alkalinisation of blood using sodium bicarbonate($NaHCO_3$): Used as alternative to oximes in places like Iran and Brazil. Mechanism of action: is unknown although increasing pH to more than 7.50 by $NaHCO_3$ may lead to destruction of OP molecules (reported to improve outcome in dogs).

Other possible benefits of $NaHCO_3$ use:

- ❖ Increase in excretion of drugs that are weak acids is seen by achieving pH 7.45 or more.
- ❖ Prevents cardio-respiratory arrest.
- ❖ Increase oximes bio-availability and hence increase their efficacy.
- ❖ Potentiates atropine action in acute organophosphate poisoning.
- ❖ It may have direct effect on neuromuscular junctional functions.

15. Use of foetal bovine or equine or human serum AChE

- It is Organophosphate scavenger.

Disadvantage: - not useful in self poisoning.

- Outcome is not of any benefit.

16. Hemodialysis and Hemofiltration:

    Role in OP poisoning not yet clear but may be useful. It is useful in dichlorovas poisoning because it is less lipid soluble.

17. Use of recombinant bacterial Phosphotriesterases , or hydrolases as bio scavenger (exogenous enzymes to sequester OP compounds.)
18. Antioxidants:It is useful because it prevents free radical generation, and also use of selenium benefits in this regard.

19. Gacyclidine: antiglutamatergic compound that was beneficial when-combined with atropine, pralidoxime, and diazepam in nerve agents poisoning.

1. **COMPLICATIONS AND ITS TREATMENT** :

- Pulmonary edema: This persists even after full atropinisation or may occur after abrupt stopping of atropine hence patient should be closely monitored and Furosemide is considered in such scenarios and treated as case of acute respiratory distress syndrome.

- Respiratory failure: It occurs due to poisoning per se or induced due to aberrant administration of pralidoxime hence respiratory depression is closely watched for and patient is promptly intubated and put on mechanical ventilation during resuscitation.

- Hydrocarbon pneumonitis occurs in patients who have ingested liquid concentrates of OP pesticides hence good and proper history helps in early recognition, prevention and treatment mainly by pulmonary ventilation assistance and antibiotic cover.

- Seizures: Convulsions occur rarely in patient inspite of atropine and pralidoxime administration due to severe poisoning. The benzodiazepines (diazepam *or* lorazepam) are the agents of choice as initial therapy. Intra osseous (Bone injection Gun,BIG) midzolam demonstrated rapid peak concentration in swine compared to IV or IM route, can be used to control convulsions.

Injected OP poisoning:

- Injected OP compounds lead to severe toxicity and require higher doses of antidotes.

- Local tissue necrosis may occur at the site of injection which may need surgical intervention.

Role of prophylactic treatment in people (farmers, agricultural scientists) who are risk of exposing themselves to OP compounds.

There is no role and also any benefit in administering atropine or pralidoxime prophylactically to workers as it may mask organophosphate poisoning's early signs and symptoms .

COMPLICATIONS:

- Can occur upto 43% of cases of acute intoxication.
- Death can often occur early (within 24 hours) in untreated cases; after variable periods up to 10 days in those who reach a hospital and are given optimal management.

Early deaths are mostly related to

1) CNS depression
2) Seizures
3) Ventricular arrhythmias
4) Respiratory failure due to

- Excessive bronchial secretions
- Bronchospasms
- Pulmonary oedema
- Paralysis of respiratory muscles or
- Apnoea associated with depression of the medullary respiratory centre

Late mortality is caused by

1. Respiratory failure – associated with

- Infection
- Pneumonia
- Septicaemia

2. Complications related to protracted period of mechanical ventilation and intensive care management.
3. Late unexpected ventricular arrhythmias, respiratory failure, sudden collapse and death may occur.

Respiratory failure is the most common complication following acute OP poisoning.

OTHER COMPLICATIONS :

Liver function abnormalities, blood dyscrasias, coagulopathy,pancreatitis and ulcerative stomatitis.

PROGNOSIS :

- Depends upon the dose of the poison and promptness of treatment.
- Recovery when occurs, usually complete except when irreversible CNS damage has been caused by prolonged anoxia and convulsions**.**

MORTALITY :

Commonest cause of death in acute organophosphorus poisoning is respiratory failure. Singh et al reported cardiac arrest as cause of death is 10% of cases**.** Namba reported that death in untreated cases occur within 24 hours and delayed up to 10 days in treated cases.

Complete recovery usually occurs in 10days. Mortality rate varies depending on poison used, duration after exposure, and atropinisation of all the toxins. In Indian studies mortality rate ranges between 4 to 38%. Malathion has the lowest toxicity because of rapid hydrolization of carboxyester group to products with little or no anticholinesterase activity. Fenthion has the maximum mortality.

MATERIALS AND METHODS

DESIGN:

Hospital based PROSPECTIVE study

METHODOLOGY:

The study is undertaken on the patients admitting in Intensive Medical Care unit of Coimbatore Medical College Hospital, Coimbatore during the period of study (i.e. July 2014 to July 2015). The study is proposed to be conducted after obtaining informed consent from the subjects as well as the control group. The duration of the study is one year, commencing from July 2014 and ending by July 2015.

The principal investigator, after first obtaining the informed consent from the subject to undergo the study, collects the details. All patients with history of exposure to organophosphorous compounds within 24 hours are chosen after applying inclusion and exclusion criteria. Patients were evaluated for Peradeniya organophosphorous poisoning scale and serum cholinesterase levels for assessment of severity of poisoning . Serum cholinesterase levels and peradeniya oraganophosphorous poisoning scale were studied to predict the need for ventilatory support , requirement of atropine , duration of hospital stay.

PATIENTS:

50 patients of Acute Organophosphorus Poisoning who are above the age of 12 years admitted in Intensive Medical Care Unit in Coimbatore Medical College Hospital**.**

SELECTION CRITERIA

(a) Inclusion Criteria

- Patients with history of exposure to organophosphorous compounds with in previous 24 hours with characteristic clinical manifestations of organophosphorous compound poisoning

(b) Exclusion Criteria

- Patients who receive treatment with atropine before admission
- Patients with doubtful diagnosis
- Patients with mixed poisoning with other substances
- Patients with history of serious systemic illness

SOURCE OF DATA

Data consists of primary data, collected by the principal investigator directly from the patients, who had approached the Coimbatore Medical College Hospital, Coimbatore. The subjects consist of patients admitted to the hospital.

TYPE OF STUDY

- Observational study

.

SERUM CHOLINESTERASE ESTIMATION:[84]

Principle:

Butyrylcholine iodide is hydrolysed by cholinesterase to produce thiocholine in the presence of potassium hexacyanoferrate,the absorbance decrease at 405nm is directly proportional to the cholinesterase activity in the sample.

Reagent:

RI-Buffer reagent
R II-Butyrylthiocholine iodide reagent

Sample:

Use non-hemolysin serum,Heparin or EDTA plasma
Reference Level:4850-12000 U/L

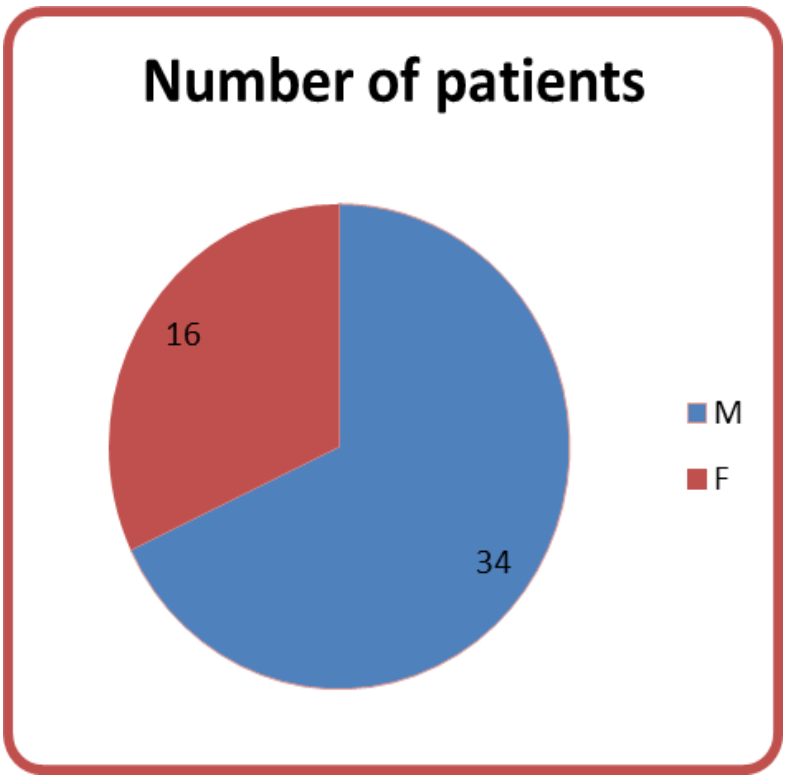
STATISTICS:

Statistical analysis Results were analyzed for statistical significance using ANOVA for both POP Scale and Serum cholinesterase with Pearson Chi-Square test.

RESULTS

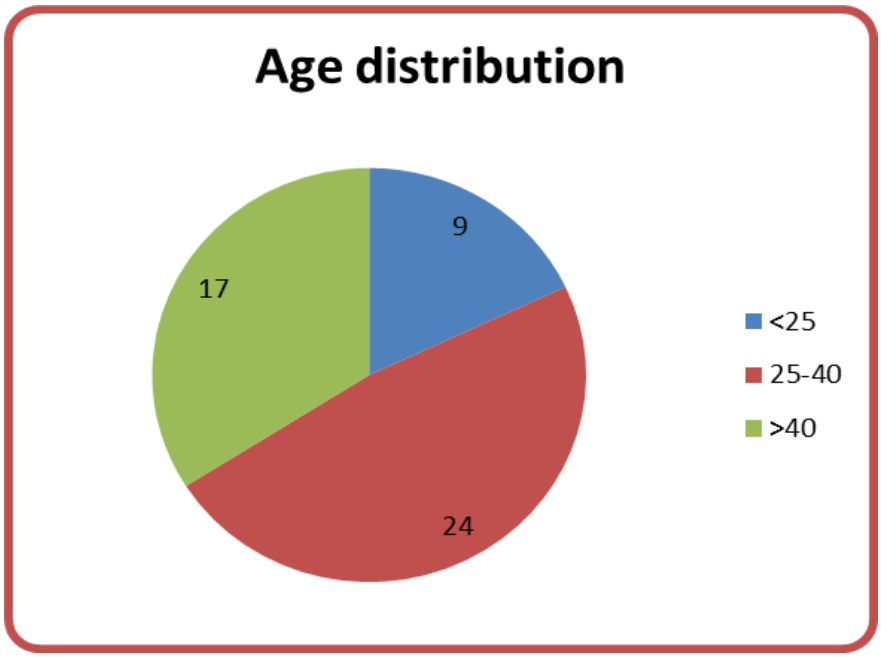
SEX DISTRIBUTION:

Sex Distribution		
Sex Distribution	**Number of patients**	**Percentage**
M	34	0.68
F	16	0.32



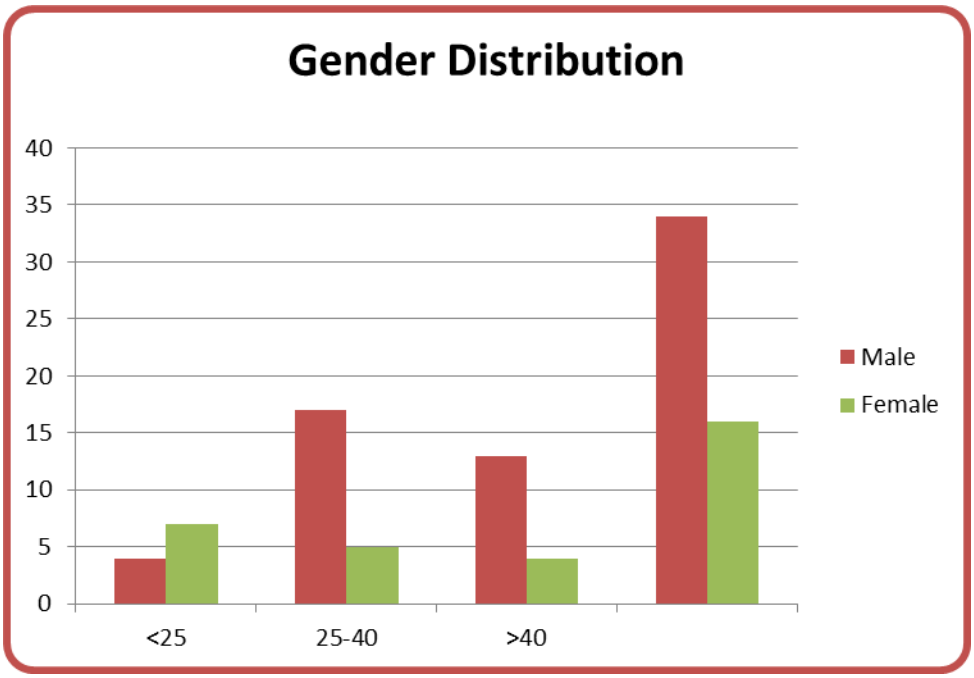
AGE DISTRIBUTION:

Age distribution		
Age distribution	**No of persons**	**%**
<25	9	18%
25-40	24	48%
>40	17	34%



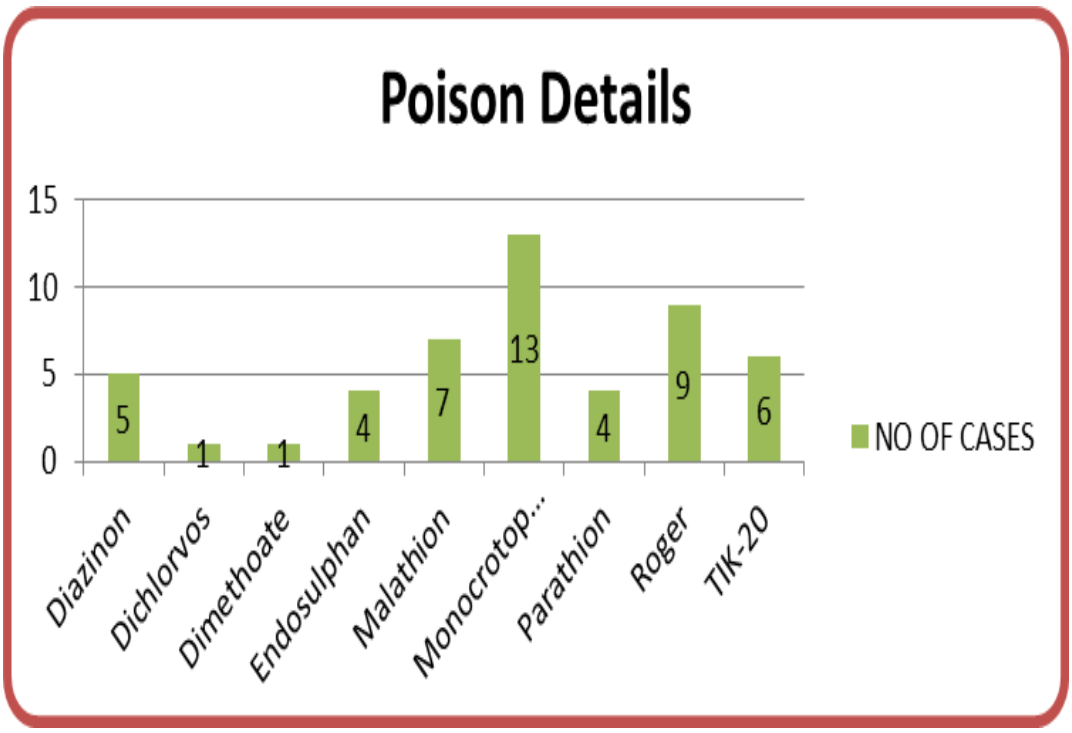
GENDER AND AGE DISTRIBUTION:

Gender and Age Distribution				
	Age(years)			Total
Sex	<25	25-40	>40	
Male	4	17	13	34
Female	7	5	4	16
total	11	22	17	50



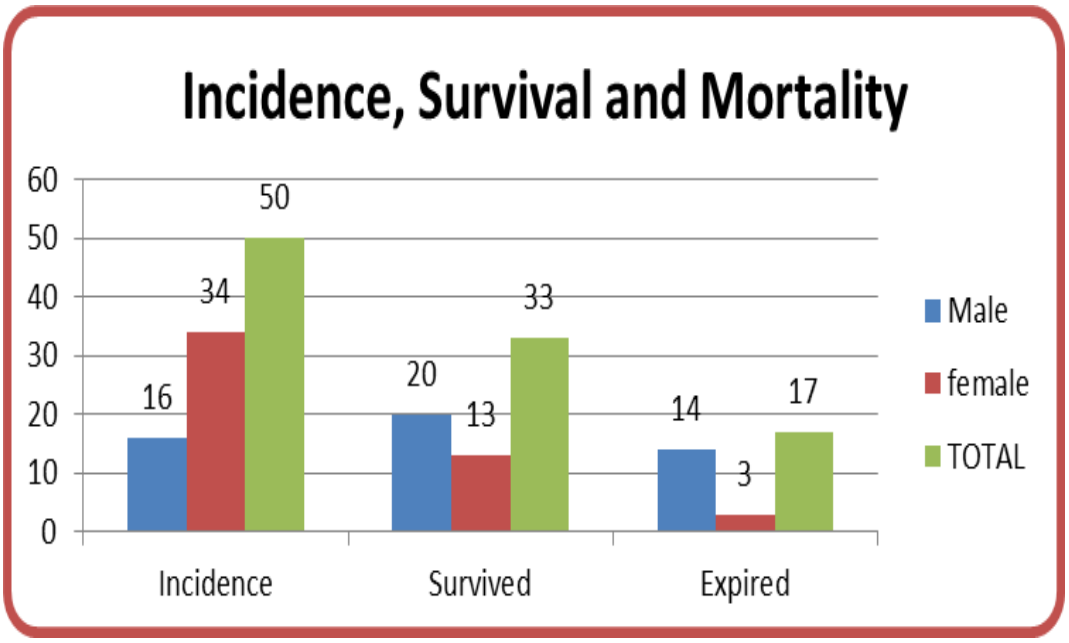
POISON DETAILS:

Poison Details		
POISON	**NO OF CASES**	**PERCENT**
Diazinon	5	10%
Dichlorvos	1	2%
Dimethoate	1	2%
Endosulphan	4	8%
Malathion	7	14%
Monocrotophos	13	26%
Parathion	4	8%
Roger	9	18%
TIK-20	6	12%



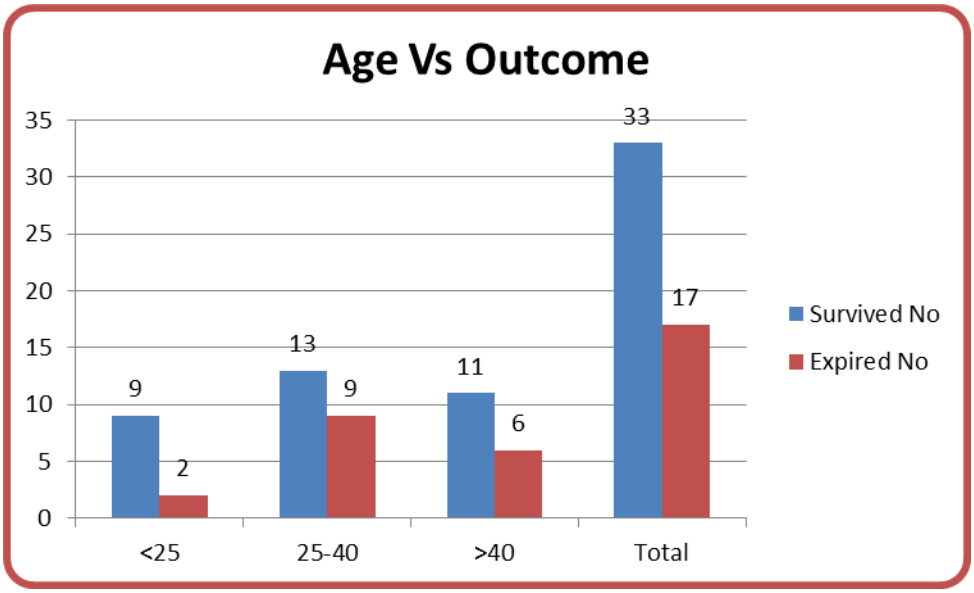
INCIDENCE, SURVIVAL AND MORTALITY:

INCIDENCE, SURVIVAL AND MORTALITY			
Sex	**Incidence**	**Survived**	**Expired**
Male	16	20	14
female	34	13	3
TOTAL	50	33	17



AGE VS OUTCOME:

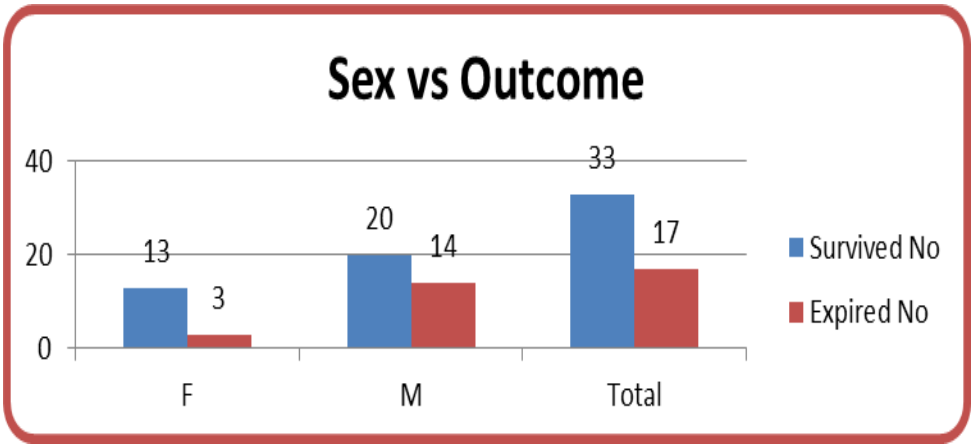
AGE Vs OUTCOME				
Age(years)	**Survived No**	**%**	**Expired No**	**%**
<25	9	27%	2	12%
25-40	13	39%	9	53%
>40	11	33%	6	35%
Total	33		17	



X^2=1.707, DF=2, P-Value=0.426

SEX VS OUTCOME:

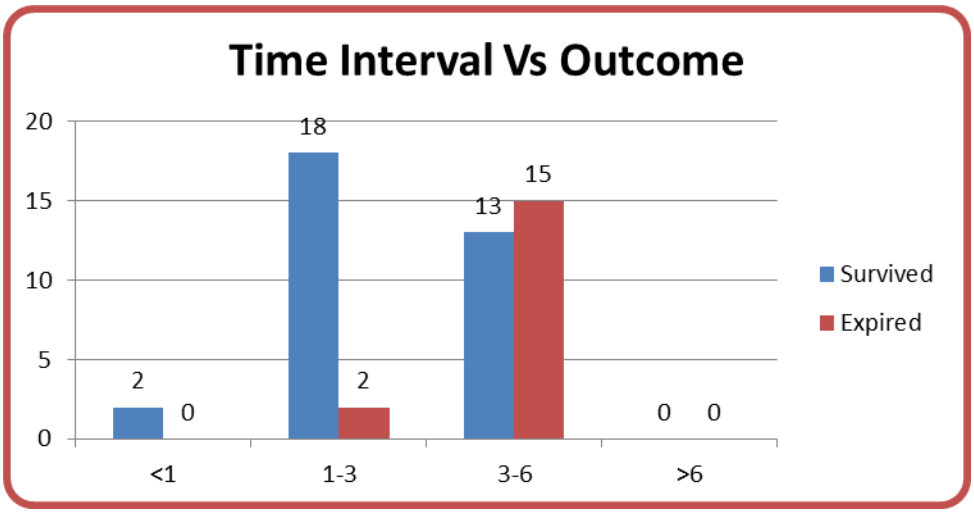
SEX Vs OUTCOME				
Sex	**Survived No**	**%**	**Expired No**	**%**
F	13	39%	3	18%
M	20	61%	14	82%
Total	33		17	



X^2=0.485, DF=1, P-Value=0.486

TIME INTERVAL VS OUTCOME:

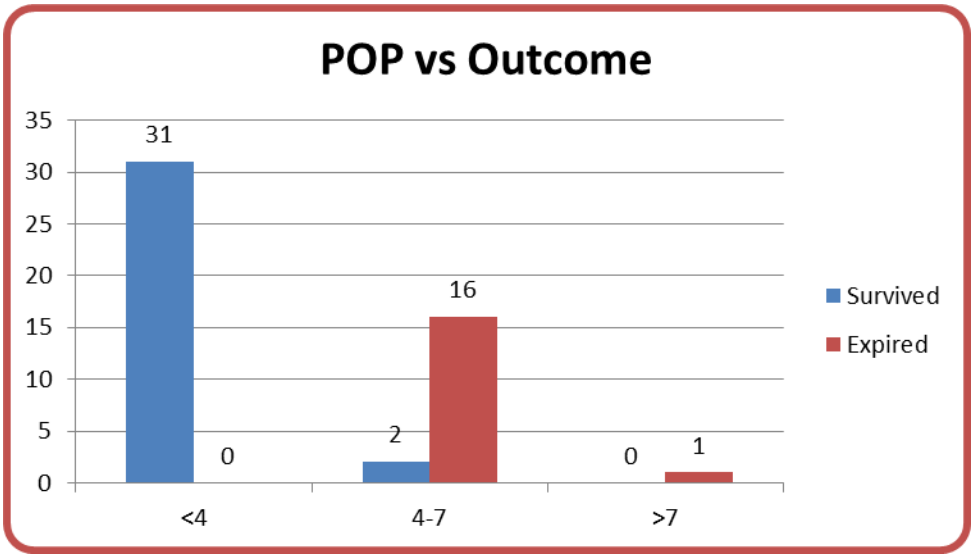
TIME INTERVAL Vs OUTCOME:				
Time interval (hours)	**Survived**	**%**	**Expired**	**%**
<1	2	6%	0	0%
1-3	18	55%	2	12%
3-6	13	39%	15	88%
>6	0	0%	0	0%



X^2=5.023, DF=1, P-Value=0.025

POP VS OUTCOME

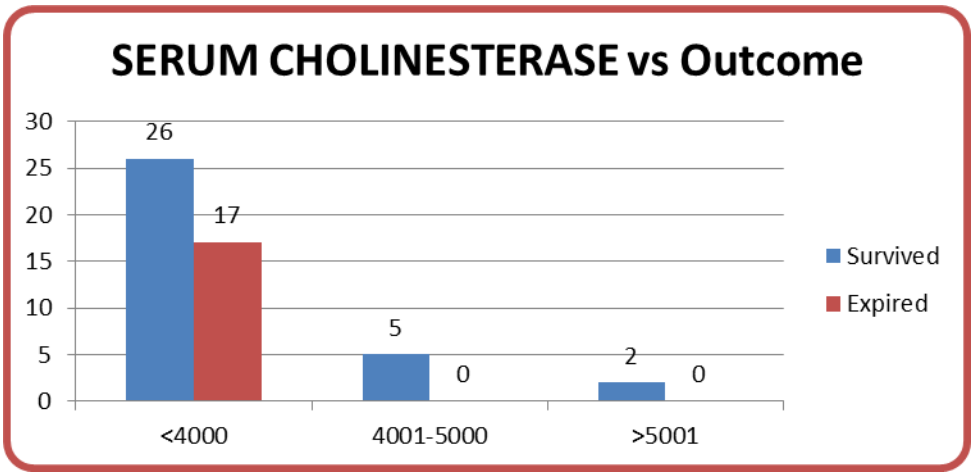
POP vs Outcome				
POP Score	**Survived**	**%**	**Expired**	**%**
<4	31	94%	0	0%
4-7	2	6%	16	94%
>7	0	0%	1	6%



X^2=13.014, DF=1, P-Value=0.000

SERUM CHOLINESTERASE VS OUTCOME:

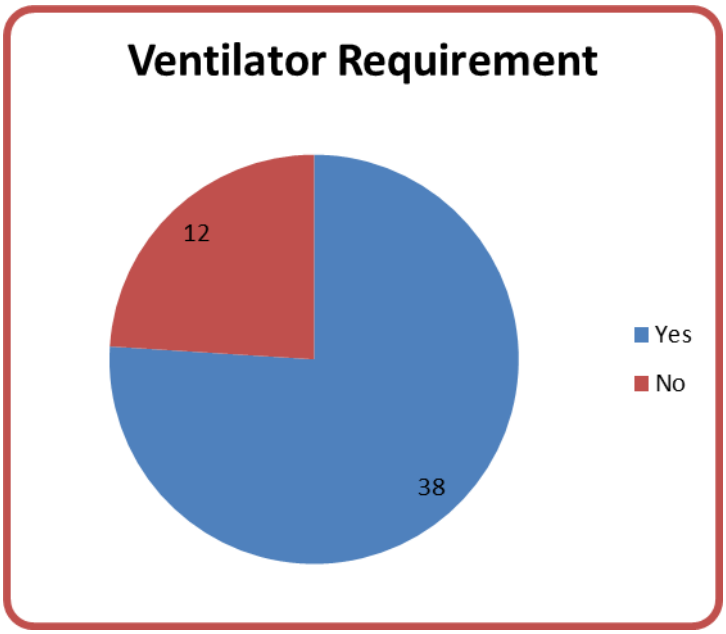
SERUM CHOLINESTERASE vs Outcome				
Serum cholinesterase	**Survived**	**%**	**Expired**	**%**
<4000	26	79%	17	100%
4001-5000	5	15%	0	0%
>5001	2	6%	0	0%



X^2=0.414, DF=1, P-Value=0.520

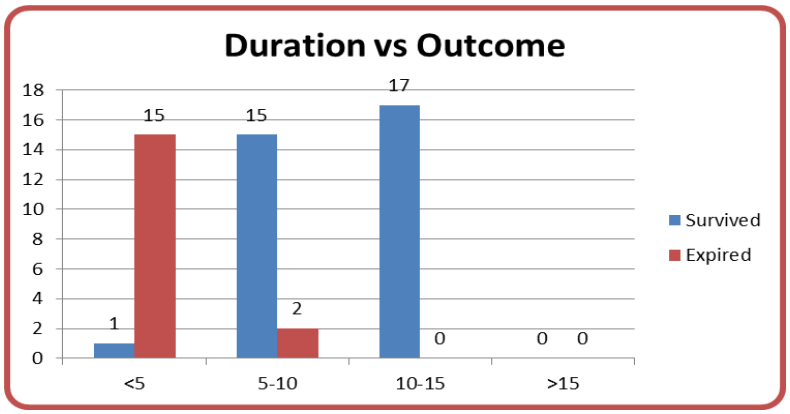
VENTILATOR REQUIREMENT:

Ventilator requirement	
Ventilator	Number of persons
Yes	38
No	12
	50



DURATION VS OUTCOME

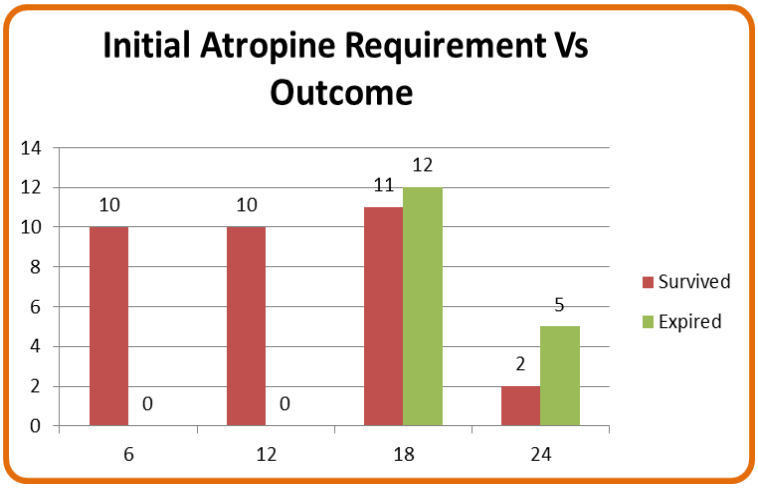
Duration Vs Outcome				
Duration (days)	**Survived**	**%**	**Expired**	**%**
<5	1	3%	15	88%
5-10	15	45%	2	12%
10-15	17	52%	0	0%
>15	0	0%	0	0%



X^2=4.466, DF=2, P-Value=0.107

INITIAL ATROPINE REQUIREMENT VS OUTCOME:

Initial Atropine Requirement Vs Outcome				
Initial Atropine Requirement	**Survived**	**%**	**Expired**	**%**
6	10	30%	0	0%
12	10	30%	0	0%
18	11	33%	12	71%
24	2	6%	5	29%



DISCUSSION

This study was conducted in Coimbatore medical college hospital from July 2014 to July 2015. A total of 50 cases were studied. The clinical and diagnostic findings of this study are compared with our studies in literature here.

PREVALENCE:

About 500 OP poisoning cases per year were reported in Coimbatore Medical College Hospital. It was around 30 cases per month. A sample of 50 cases were collected for this study. In that 2/3 cases were male patients, 1/3 are female patients. In 50 cases around 17 cases were expired mostly due to respiratory failure .

AGE OF THE PATIENT:

In our study, majority of patients were in the age group of 25-40 years (48%). 66% of patients were within 40 years of age. This is in comparison to studies done by Reihman et al , Goel et al ,and Doshi et al.

STUDY NAME	AGE GROUPS(YEARS)	PERCENTAGE(%)
Reihman et al[81]	15-25	70
Goel et al[85]	12-30	86.4
Doshi et al[82]	21-30	-
Shankar et al[88]	11-30	-
Gupta et al[89]	11-30	-
Kamath et al[90]	16-30	-
Present study	25-40	48

GENDER DISTRIBUTION:

This study revealed a male preponderance (68%), females accounting for 32% of cases. The M:F ratio in this study is 2.125:1. This almost corresponds to gender distribution reported by Goel et al (2.5:1). Shankar et al (1.48:1), Gupta et al (2.3:1).

Authors	M:F Ratio
Shankar et al[88]	2.5:1
Goel et al[85]	2.57:1
Thomas et al	1.27:1
Gupta et al[89]	2.3:1
Kamath et al [90]	1.2:1
Shoba TR et al[84]	1.3:1
Present study	2.125:1

TYPE OF POISON:

Authors	Common poison
Bhattarai N et al[86]	methyl parathion
Vikram P et al[83]	methyl parathion
Goel et al[85]	Monocrotophos
Avasthi et al	Monocrotophos
Present study	Monocrotophos followed by Roger

Monocrotophos followed by Roger was the commonly used OPC in this study which was comparable to Goel et al and Avasthi et al studies.

SEVERITY OF POISONING:

GRADE	Arup kumar kundu et al[95](%)	Present study(%)
MILD	19.5	62
MODERATE	50.9	36

SEVERE	29.6	2

In this study 62% of patients reported with mild grade of poisoning with a POP score less than 4. Only 2% of patients had a score more than 7 and had severe poisoning.

OVERALL MORTALITY:

The overall mortality in organophosphate poisoning in various studies are:

Authors	Total cases	Total deaths	Percent
Manoj et al[91]	100	17	17
Manimala et al[92]	29	04	13.79
Kabrawala et a[93]	25	03	12
Viswanathan et al[94]	168	08	4.7
Sundaram et al	-	-	23.5
Chuang FR et al	-	-	24
Present study	50	17	34

Mortality rate in present study was 34% this is comparable to Sundaram et al. and Chuang et al. In a reported literature the mortality rate ranges was 4 to 38%.

AGE AND MORTALITY:

In the present study, the mortality was 34% overall, with, 12% mortality in less than 25 years, 53% in 25-40 years ,35% in above 40 years. The mortality is higher in age groups 25-40 & above 40 years. Shankar reported maximum mortality in age group of 21-30 years (61.11%). Generally younger age group are more susceptible than older group because the enzymes like mixed functions

oxidases which metabolize organophosphorus compounds are less mature; but the older age group are more susceptible to complications like acute renal failure, sepsis, and multi-organ failure.

SEX AND MORTALITY:

In our study total number of deaths was 17 (34%). Among the dead, 14 patients were male and 3 patients were female.14 out of 34 male patients died (41% mortality). 3 out of 16 female patients died (19% mortality).Shankar et al reported more mortality in male patients (11.6%) when compared to female patients (7.93%). Our findings are consistent with previous study.

TYPE OF OP COMPOUNDS AND MORTALITY:

In our study 38.4% of patients who consumed monocrotophos were died. 55% of patients were died who consumed Roger. Mortality is high in patients who consumed dangerous compounds like monocrotophos, Roger and Endosulphan. Our findings are consistent with other studies like Shankar , Gupta and Kamath.

TIME INTERVAL AND MORTALITY:

In our study the time interval between consumption of poison and hospital admission ranged from less than 1hour to more than 6 hours. There was less mortality in patients who came within 1 hour. Mortality was highest (88%) when patients were admitted after 3-6 hours following ingestion of pesticide. In patients who were admitted between 1 hour to 3 hours following ingestion of poison, the mortality was 12% .Our findings are consistent with Gupta et al

who reported increased mortality with increasing time interval between hospital admission and consumption of poison(39). However Karnik VM and Sunder Ram J observed no correlation between severity and time interval.

SERUM CHOLINESTERASE AND MORTALITY:

The maximum Serum cholinesterase level at admission was 5670 units while minimum level was 95 units. The overall mean Serum cholinesterase level at admission was 1669 U/L. Mean Serum cholinesterase level in survivors at admission was 2604.5 U/L whereas it was 313.78 in non-survivors. Value p is = 0.520 ($p < 0.05$ is considered as statistically significant). In majority of patients on admission it was observed that the enzyme activity was very low. Hence it can be inferred that low Serum cholinesterase activity can be taken as good diagnostic test for OP poisoning. Studies by Namba T et al and Wadia R.S et al has also shown that Serum cholinesterase activity estimation is a reliable diagnostic test in OPC poisoning. Observations from this study shown that patients with higher Serum cholinesterase activity on day of admission has a better prognosis than with lower enzyme values. Initial estimation of Serum cholinesterase activity can be used to predict the prognosis of patients. Recent studies by Kuppuswamy G et al showed that Serum cholinesterase activity below 10% of normal were associated with poor prognosis. He also observed that Serum cholinesterase in plasma is more sensitive than AChE to inhibition by a number of compounds and is depressed well below the normal range of 60% before any symptoms due to systemic anticholinesterase intoxication is evi-

dent. Data from patients who died showed that out of 19 patients who expired majority had enzyme value around 300 U/L, which is lower limit. These observations shows that lower the levels of enzyme at admission the more is the mortality.

CONCLUSIONS

- OP poisoning is the most common modes of suicidal deaths in our country.
- Poisoning is confirmed by biochemical investigation.
- The M:F ratio in this study is 2.125:1.
- Middle age groups between 25-40 years are more commonly encountered in poisoning by organophosphate compounds.
- Majority had consumed poison orally.
- Mortality in our study was 34%.
- There is higher mortality with organophosphate like Monocrotophos and Roger which are categorized as highly lethal compounds.
- There was good correlation between POP Scale and serum cholinesterase levels on admission and severity of poisoning.
- Serum cholinesterase levels were significantly depressed in patients who was in severe poisoning. Low levels of enzymes in early stages of poisoning indicates increased mortality.
- In early stages of poisoning determining serumcholinesterase activity form a reliable diagnostic test.
- Mean cholinesterase activity in patients who survived was above 2604.5 U/L In the patients who expired the cholinesterase activity was around 313.78 U/L. This point out that enzyme levels is directly proportional to better prognosis.

SUMMARY

- 50 cases of OP poisoning admitted to Coimbatore Medical College Hospital between July 2014 – July 2015 were included in the study.
- Commonest age group involved is above 25 years.
- Males are the most common victims (68%).
- Majority of patients admitted within 6 hours of exposure.
- Malathion and roger were the most common compounds used by the patients for poisoning.
- 86% had mild, 10% had moderate and 4% had severe degree of poisoning according to serum cholinesterase level.
- 62% had mild, 36% had moderate and 2% had severe degree of poisoning according to POP Scale.
- Mortality was least among the patients who presented to the hospital early as compared to those who presented late.
- Patients who had lower level of serum cholinesterase within 24hrs had increased mortality.
- Overall mortality was (34%).
- Serum cholinesterase levels correlated well with severity of poisoning and outcome.
- POP Scale also correlated with severe poisoning.
- The correlation of POP scale and serum cholinesterase levels help in predicting the ventilatory support, atropine requirements and duration of hospital stay.

BIBLIOGRAPHY

1. Zhao X, Wu C, Wang Y, Cang T, Chen L, Yu R, et al. Assessment of toxicity risk of insecticides used in rice ecosystem on Trichogramma japonicum, an egg parasitoid of rice lepidopterans. J Econ Entomol. Feb 2012;105(1):92-101.
2. Chen SW, Gao YY, Zhou NN, Liu J, Huang WT, Hui L, et al. Carbamates of 4'-demethyl-4-deoxypodophyllotoxin: synthesis, cytotoxicity and cell cycle effects. Bioorg Med Chem Lett. Dec 15 2011;21(24):7355-8.
3. Peter JV, Cherian AM. Organic insecticides.Anaesthesia and intensive care 2000;28(1) :11-21
4. WHO in collaboration with UNEP, 1990. Public Health Impact of Pesticides used in Agriculture. Updated June 2007, WHO, Geneva.
5. Eddleston M, Phillips MR. Self poisoning with pesticides. BMJ. Jan 3 2004;328(7430):42-4.
6. Weiss M, Parker S. Suicide. In : Desjarlais R, Eisenberg L,Good B, Kleinman A, editors. World mental health.Problems and priorities in low-income countries .New York : Oxford University Press; 1995 p. 68-86.
7. Siwach SB, Gupta A. The profile of acute poisonings in the Haryana-Rohtak study. J Assoc Physicians India 1995;43 : 756-9

8. Lifshitz M, Shahak E, Sofer S. Carbamate and organophosphate poisoning in young children. Pediatr Emerg Care. Apr 1999;15(2):102-3.
9. Ohayo-Mitoko GJ, Heederik DJ, Kromhout H, Omondi BE, Boleij JS. Acetylcholinesterase inhibition as an indicator of organophosphate and carbamate poisoning in Kenyan agricultural workers. Int J Occup Environ Health 1997;3:210-20.
10. Chaudhry R, Lall SB, Mishra B, Dhawan B. A foodborne outbreak of organophosphate poisoning. BMJ 1998;317:268-9.
11. Palmer Taylor. Anticholinesterase agents, Goodman-Gilman's The pharmacological basis of therapeutics 9th ed, McGraw Hill, New York 1996;160.
12. Orfila MJB Traite des poisons tines mineral, vegetal et animal on toxicology generale sous le rapports de la medicine legale Paris: Crochard;1815.
13. .Stedman E. Chemical constitution and miotic action, Am. J. Physiol. 1929;90:528-529
14. Schrader G. Die entwickling rever insektizide auf Grindlange von organischem fluoro und phosphor verbindingen. Monographic No.62 Verlag Chemie, Winheim 1952.
15. Wilson B. Acetyl cholinesterase XIReversibility of TEPP inhibition. J. Biochem 1951;190:111-117

16. Besser RG. Intoxication with organophosphorus compounds. Vinken PJ, Bruyen GW, editors. Intoxications of the Nervous System. Amsterdam, The Netherlands: Elsevier Science Publishers; 1989. p. 151-81.
17. John.P.Morgan.M.D.The Jamaican Ginger Paralysis, JAMA, 1982;248(15);1864-1867.
18. en .wikipedia.org/wiki/Organophosphate.
19. Vishwanath et al. Bug poison poisoning. JIMA 1962;39(1) 345-349
20. Advanced Studies on the Synthesis of Organophosphorus Compounds UNIVERSITÀ DI BOLOGNA
21. Doshi JC,Katakia MK,Baxamusa HM.Organophosphorous poisoning-A review with study of 25 cases J postgraduate Med Aug 1964;XI.2:62-78.
22. Inactivation of cholinesterase by compounds related to neostigmine.LEVIN AP, JANDORF BJ. J Pharmacol Exp ther 1955 Feb;113(2):206-11.
23. Cholinesterase reactivator. Prepn of salts: I. B. Wilson et al., US 2816113 (1957 to U.S. Sec'y. of Army);
24. Maroni M. Review of toxicological properties and biotransformation of organophosphorus esters in: WHO manual of analytical methods, Cremona 1985; 3:39.
25. Davies JE. Changing profile of pesticide poisoning. New England Journal of Medicine 1987;316 :806-808.
26. Management of acute organophosphorus pesticide poisoning

27. Gordon. HA. Sharpio SD.Benson : Forensic Medicine-A guide to Principles 3rd edition
28. Taylor P.Anticholinergic agents in:Goodman Gilman:The pharmacological basis of therapeutics Newyork;Mac Milan 1985;110-129.
29. Davies JE. Changing profile of pesticide poisoning. New England Journal of Medicine 1987;316 :806-808.
30. Haddad LM. Organophosphates and other insecticides. In: Haddad LM, Winchester J, Eds. Clinical management of poisoning and drug overdose. W.B.Saunders company 1990: 1076-87.
31. Lotti M.Clinical toxicology of acetylcholinesterase agents in humans. In Krieger RI,Doull J,eds.Handbook of pesticide toxicology.San diego: academic press,2001:1043-1085.
32. Davies DR, Green AL: The kinetics of reactivation by oximes of cholinesterase inhibition by organophosphorus compounds. Biochemical Journal 1956; 63: 529-35
33. Worek F, Backer M, Thiermann H, et al. Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. Hum Exp Toxicol1997; 16:466–72.
34. http://virtual.yosemite.cc.ca.us/rdroual/Course%20Materials/Physioogy%20101/Chapter%20Notes/Fall%202011/chapter_11%20Fall%202011.htm.
35. Guyton Ac, Hall JE. Textbook of medical physiology.2011:80-84,690-708

36. Source=Originally from [http://es.wikipedia.org
37. Basic & Clinical Pharmacology 11th ed. By Katzung et al.
38. Peck and Hill Pharmacology for Anaesthesia and Intensive care
39. Handbook of Pharmacology and Physiology in Anaesthetic Practice by Stoelting and Hillier.
40. Churchill Davidson Wylie: A practice of Anaesthesia 6th edition
41. Wadia RS, Ichaporea Rn, Karnik VM, Belwani GS, Grait KB. Cholinesterase levels in diazinin poisoning and after atropine treatment. JAMA 1972;59:234-37.
42. Mehta AB, Shach AC, Joshi LG, Kale AK, Vora DD. Clinical features and plasma cholinesaterases activity in poisoning with insecticidal organophosphorous compounds. JAPI 197;19:18
43. Thomas Chang Yao-Tsao, Yeong-Chang Juang et al. Respiratory failure of acute organophosphate and carbamate poisoning. Chest 1990;98(1):631-635.
44. Wadia RS. et al. Neurological manifestation of the organophosphorus compounds IJMR 1977;66:460 -68.
45. Dagli AJ, Shaikh WA. Pancreatitis involvement in malathion- anticholinesterase insecticide poisoning-a study of 75 cases. British Journal of Clinical Practice. 1983;37:270-272. Hsiao CT, Yang CC, Deng JE, Bullard MJ, Liaw SJ. Acute Pancreatitis following organophosphate poisoning. Journal of Toxicology-Clinical Toxicology 1996;34:343-347.

46. Hui KS. Metabolic disturbances in organophosphate insecticide poisoning. Arch Pathol Lab Med. 1983;107(3):154.
47. Matsumiya N, Tanaka M, Iwai MN, Kondo T, Takahashi S,Sato S. Elevated amylase is related to the development of respiratory failure in organophosphate poisoning. Human and Experimental Toxicology 1996;15:250-253.
48. Stedman E. Chemical constitution and miotic action. Am. J. Physiol. 1929;90:528-529.
49. Poojara L,Vasudevan D, Arun Kumar AS, Kamat V. Repetitive nerve stimulation(RNS) for Intermediate syndrome. IJCCM 2003;7(2):94-102.
50. Karalliedde L. Organophosphate poisoning and anaesthesia. Anaesth 1999;54:1078
51. Namba T, Nolte CT, Jackrel J, Grob D. poisoning due to OP insecticide,American Journal of Medicine 1971:50:475-492
52. Clinical management of poisoning and drug over dosage – pesticides 3rd ed W.B. Saunders;1998:838-845.
53. Grob D , John RJ.Treatment of Anticholinesterase intoxication with oximes.JAMA 1958;166:1855.
54. Driesbach R.H.Handbook of poisoning-Diagnosis and treatment 2nd edition 1957:87.
55. Balani SG. Et al. Diazinon poisoning-A report of 100 cases with particular reference to evaluation of treatment. JAPI 1968.

56. Patel et al. Predictors of mortality in organophosphorus compound poisoning. JAPI 1996:44(19):951.
57. Senanayake N, De Silva H J, Karalliedde L.A scale to assess the severity of organophosphate poisoning. POP scale. Hum Exp Toxicol 1993; 12; 297-299.
58. Bardin PG, Van Eeden SF. Organophosphorus poisoning: grading the severity and comparing treatment between atropine and glycopyyrolate. Crit Care Med 1990:18:956-60.
59. Petroianu GA. Poisoning with organophosphorus compound (OPC): Mythology vs. Reality. The Middle East J Emer Med 2006; 6: 3-8.
60. http://www.drugswell.com/winow/+winowDrug%20Overdose/11192162-poisoning-and-drug-overdose-4th-edition.htm
61. Wadia RS. Treatment of organophosphate poisoning. Editorial. IJCCM April-June 2003; 7(2) 85-87.
62. Haywood PT, Karalliedde L. Management of poisoning due to organophosphorus Morentensen ML.
63. Management of acute childhood poisoning caused by selected insecticides and herbicides. Paediatrics Clinics of North America 1986;33:421-445.
64. Dutoit PW et al. Experience with the intensive care management of organophosphate insecticide poisoning. South African Med. Journal 1981;60:227-229.

65. Burdin PG, van Eaden SF. Organophosphate poisoning : grading the severity and comparing treatment between atropine and glycopyrrolate. Crit Care Med 1990;18:956-960.
66. Vishwanathan M et al. Treatment of organophosphorus compound poisoning. JIMA vol.43 No.10 494-495.
67. Kabrawala et al. Pralidoxime chloride as an adjunct in treatment of diazinon poisoning. JAPI 1971;19:273-277.
68. Sidell FR. Et al. Intramuscular and intravenous administration of small doses of 2 pyridinium aldoxime methochloride in man. Journal of Pharmaceutical Sciences 1971;60:1224-1228.
69. Lewis R, Goldfrank. Insecticides –organophosphate andcarbamated compounds in Goldfrank toxicology emergencies 3rded, Appleton and Lange 1994:1105.
70. WHO Technical series No.227 1962. Toxic hazards of pesticides to man, 12th report of expert committee on insecticides:27-30.
71. Lockridge O, Eckerson H. W, La Du NN. Interchain disulfide bonds and subunit organization in human serum cholinesterase. J. Biol. Chem 1979;279:324-330.
72. Haywood PT, Karalliedde L. Management of poisoning due to organophosphorus compounds. Current Anaesthesia and Critical Care 2000;11:331-337.
73. Martinez-Chuecos J et al. Experience with hemoperfusion for organophosphate poisoning. Crit Care Med 1992;20:1538-1543.

74. Matsumiya N, Tanaka M, Iwai MN, Kondo T, Takahashi S,Sato S. Elevated amylase is related to the development of respiratory failure in organophosphate poisoning. Human and Experimental Toxicology 1996;15:250-253.
75. Haywood PT, Karalliedde L. Management of poisoning due to organophosphorus compounds. Current Anaesthesia and Critical Care 2000;11:331-337.
76. Pichamuthu K, Jerobin J, Nair A, et al. Bioscavenger therapy for organophosphate poisoning - an open-labeled pilot randomized trial comparing fresh frozen plasma or albumin with saline in acute organophosphate poisoning in humans. Clin Toxicol (Phila). 2010;48(8):813-9.
77. Pazooki S, Solhi H, Vishteh HR, et al. Effectiveness of fresh frozen plasma as supplementary treatment in organophosphate poisoning. Med J Malaysia. 2011;66(4):342-5.
78. Blain PG. (2011). Organophosphorus poisoning (acute). Clin Evid. [Online] Available from www.ncbi.nlm.nih.gov/pubmed/21575287. [Accessed February, 2012].
79. Perera PM, Jayamanna SF, Hettiarachchi R, et al. A phase II clinical trial to assess the safety of clonidine in acute organophosphorus pesticide poisoning. Trials. 2009;10:73.
80. Eddleston M, Juszczak E, Buckley NA, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. Lancet. 2008;371(9612):579-87.

81. Aaron C K, Howland M A. Insecticide: Organophosphates and Carbamates. Goldfrank Toxicological Emergencies, Gold frank L.R., Flomenbaum NE et al, 6th ed, Appleton and Lange, 1998,1429-1449.
82. Karalliedde L, Sananayake N. Organophosphorous Insecticide Poisoning. Br J Anaesthesia 1989;63:736-750.
83. Vasanaik M. Organophosphate and organocarmate poisoning-Controversies in management.The Indian Practitioner 2001;54:340-346.
84. Clinical management of poisoning and drug over dosage – pesticides 3rd ed W.B. Saunders;1998:838-845.
85. Bardin PG, Van Eeden SF. Organophosphorus poisoning: grading the severity and comparing treatment between atropine and glycopyyrolate. Crit Care Med 1990:18:956-60.
86. Petroianu GA. Poisoning with organophosphorus compound (OPC): Mythology vs. Reality. The Middle East J Emer Med 2006; 6: 3-8
87. Evaluation of suspected chronic pesticide poisoning,Biomedica Vol.23 Jul-dec.2007/Bio-1pg 77.
88. Wang R, Tang XC (2005). "Neuroprotective Effects of Huperzine A.". Neurosignals 14 (1-2): 71–82.
89. Leuzinger W, Baker AL (February 1967). "Acetylcholinesterase, I. Large-scale purification, homogeneity, and amino acid analysis". Proc. Natl. Acad. Sci. U.S.A. 57 (2): 446–451. doi:10.1073/pnas.57.2.446. PMC 335526. PMID 16591490.

90. Leuzinger W, Baker AL, Cauvin E (February 1968). "Acetylcholinesterase. II. Crystallization, absorption spectra, isoionic point". Proc. Natl. Acad. Sci. U.S.A. 59 (2): 620–3. doi:10.1073/pnas.59.2.620. PMC 224717. PMID 5238989.
91. Sussman JL, Harel M, Frolow F, Oefner C, Goldman A, Toker L, Silman I (August 1991). "Atomic structure of acetylcholinesterase from Torpedo californica: a prototypic acetylcholine-binding protein". Science 253 (5022): 872–9. doi:10.1126/science.1678899. PMID 1678899.
92. Huang YJ, Huang Y, Baldassarre H, Wang B, Lazaris A, Leduc M, Bilodeau AS, Bellemare A, Côté M, Herskovits P, Touati M, Turcotte C, Valeanu L, Lemée N, Wilgus H, Bégin I, Bhatia B, Rao K, Neveu N, Brochu E, Pierson J, Hockley DK, Cerasoli DM, Lenz DE, Karatzas CN, Langermann S (August 2007). "Recombinant human butyrylcholinesterase from milk of transgenic animals to protect against organophosphate poisoning". Proc. Natl. Acad. Sci. U.S.A. 104 (34): 13603–8.
93. Brash: Clinical Anesthesia, 5th ed, pp 546-549
94. Miller: Anesthesia, 6th ed, pp 487-488.
95. Sullivan JB and Blose J. Organophosphate and carbamate insecticides. In: Sullivan JB and Krieger GR (eds), Hazardous Materials Toxicology. Baltimore, MD: Williams and Wilkins,1992, pp. 1015-26.

ANNEXURES

Proforma

Name		Age	
Occupation		Sex	
Socio Economic status		IP No	
Address			
Date and Time of consumption		Date and Time of admission	
Poison Details			

Peradeniya organonphosphorus poisoning (POP) scale

SL NO	PARAMETER		SCORE	PATIENT SCORE
1	MIOSIS	Pupil size >2mm	0	
		Pupil size ≤2mm	1	
		Pupils pin point	2	
2	FASCICULATIONS	None	0	
		Present but not general-ized or continuous	1	
		Generalized and continu-ous	2	
3	RESPIRATION	Respiratory rate ≤20/min	0	
		Respiratory rate >20/min	1	
		Respiratory rate >20/min with central cyanosis	2	
4	BRADYCARDIA	Pulse rate >60/min	0	

		Pulse rate 41-60/min	1	
		Pulse rate ≤40/min	2	
5	LEVEL OF CON-SCIOUSNESS	Conscious and rational	0	
		Impaired, responds to verbal commands	1	
		Impaired, no response to verbal commands	2	
6	CONVULSION	present	1	
	Total Score		11	

INITIAL ATROPINE DOSAGE FOR ATROPINIZATION _ mg

24 hour Atropine dosage Requirement:

Serum cholinesterase level: U/L

Requirement of mechanical ventilation: Yes/No

Duration of stay in hospital:

Incase of death, cause of death:

CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled "CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME OF ORGANOPHOS-PHOROUS COMPOUND POISONING""in CMC Hospital, Coimbatore, conducted by DR.SHALINI.M., Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

"CORRELATION OF POP SCALE AND SERUM CHOLINESTERASE LEVEL IN ASSESSING THE CLINICAL SEVERITY AND OUT-COME OF ORGANOPHOSPHOROUS COMPOUND POISONING"

Purpose of Research

To assess the correlation of POP scale and serum cholinesterase level in predicting

1.The clinical severity and outcome of organophosphorous compound poisoning

2.To predict the need for ventilatory support , requirement of atropine , and duration of hospital stay

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

----------	----------
Signature /Left thumb impression (volunteer)	Date
----------	----------
Signature of witness	Date

MASTER CHART

SL NO	IP. NO.	NAME	DATE OF ADMN.	AGE	SEX	Address	OCCUPATION	POISON DETAILS	QUANTITY CONSUMED	TIME INTERVA BETWEEN CONSUMPTION AND AD-MISSION	POP SCORE	SERUM CHOLINESTERASE	INITIAL ATROPINE RE-QUIREMENT	24 HOURS ATROPINE RE-QUIREMENTS	VENTILATORY SUPPORT	DURATION OF HOSPITAL STAY	OUTCOME	CAUSE OF DEATH
1	29564	David	3.8.14	24	M	Sulur	Labourer	Roger	20	4	1	2340	6	48	No	8	S	
2	29836	Sivasamy	8.8.14	65	M	Puliampatti	Farmer	Dimethoate	15	2	1	3450	6	48	No	5	S	
3	41103	Ramasamy	15.8.14	50	M	Pongalur	Farmer	Monocrotophos	60	6	5	1430	18	48	Yes	5	E	Aspiration pneumonitis
4	41126	Laksmi	15.8.14	25	F	Udumalai	Housewife	Roger	30	6	4	1200	12	48	Yes	12	S	
5	42024	Leena	2.10.14	29	F	Annur	Housewife	Endosulphan	40	4	6	325	24		Yes	1	E	Respiratory failure
6	42202	Gokila	9.10.14	16	F	Somanur	Student	Dichlorvos	25	3	0	4200	6	48	No	10	S	
7	42209	Kalaiselvan	9.10.14	33	M	Annur	Farmer	Endosulphan	50	4	5	154	18	60	Yes	2	E	Respiratory failure
8	43587	Umshalma	16.10.14	50	F	Pothanur	Housewife	Monocrotophos	30	4	4	1235	18	48	Yes	14	S	
9	43726	Kunja	23.10.14	45	F	Selvapuram	Housewife	TIK-20	25	2	1	4587	12	48	No	10	S	
10	43797	Sivakumar	30.10.14	28	M	Pothanur	Labourer	Malathion	15	3	1	5630	12	48	No	10	S	
11	44317	Bakyalakshmi	30.10.14	47	F	Gandhipuram	Labourer	Monocrotophos	30	2	3	3480	18	48	Yes	12	S	
12	44541	Mani	4.11.14	58	M	Sitapudur	Labourer	Diazinon	50	3	6	345	18	48	Yes	3	E	Respiratory failure
13	44783	Krishnan	4.11.14	47	M	Saibaba colony	Labourer	Parathion	20	3	4	1230	24	48	Yes	15	S	
14	44862	Velliangiri	5.11.14	40	M	Tiruppur	Labourer	Monocrotophos	70	4	7	291	18	60	Yes	2	E	Respiratory failure
15	45108	Shankar	11.11.14	46	M	Alangudi	Farmer	Roger	60	4	7	154	24		Yes	1	E	Respiratory

																		failure
16	45471	saranya	18.11.14	20	F	Puliakulam	Housewife	Monocrotophos	15	1	2	1124	24	48	Yes	10	S	
17	45832	Gokul	24.11.14	21	M	Vadavalli	Student	Monocrotophos	10	2	2	3200	18	48	Yes	14	S	
18	46780	Ganesan	24.11.14	24	M	Navavur	Driver	TIK-20	10	4	1	1256	18	48	Yes	12	S	
19	46809	Salim	2.12.14	37	M	Marudamalai	Labourer	Malathion	10	6	1	5670	6	48	No	8	S	
20	46833	Kumarasamy	9.12.14	80	M	Dharapuram	Farmer	Roger	55	6	6	324	18	48	Yes	5	E	Respiratory failure
21	47204	Sakthivel	9.12.14	32	M	Palani	Labourer	Diazinon	60	5	7	95	18		Yes	1	E	Respiratory failure
22	47501	Rajasekaran	16.12.14	47	M	Sastri nagar	Labourer	Parathion	25	3	0	4300	6	48	No	10	S	
23	47824	Gopalakrishnan	23.12.14	30	M	Ooty	Coolie	Endosulphan	10	6	2	1243	12	48	Yes	15	S	
24	48667	Gopi	23.12.14	38	M	Townhall	Labourer	Monocrotophos	15	2	4	879	12	48	Yes	10	S	
25	48086	Madhavan	30.12.14	45	M	Peelamedu	Coolie	TIK-20	15	3	4	1564	12	48	Yes	10	S	
26	51572	Sandhya	30.12.14	21	F	Tiruppur	Housewife	Malathion	15	6	0	1450	6	48	No	9	S	
27	51788	Moses	8.1.15	37	M	Palladam	Farmer	Diazinon	20	5	0	4560	6	48	No	7	S	
28	50888	Ravi	22.1.15	35	M	Guddalore	Coolie	Roger	50	6	6	343	18	48	Yes	4	E	Respiratory failure
29	51968	Vasanthy	22.1.15	19	F	Anaikatti	Student	Parathion	20	6	1	1245	6	48	No	8	S	
30	52112	Rukmani	29.1.15	43	F	Perur	Housewife	Monocrotophos	25	2	3	564	12	48	Yes	15	S	
31	52039	Karthik	29.1.15	30	M	Palladam	Farmer	Monocrotophos	75	6	7	112	18		Yes	1	E	Respiratory failure
32	52189	Prakash	29.1.15	35	M	Palladam	Farmer	TIK-20	30	3	4	321	18	48	Yes	12	S	
33	52200	Raja	3.2.15	29	M	Udumalai	Farmer	Malathion	20	6	4	1456	18	48	Yes	12	S	
34	52209	Kanagaraj	3.2.15	59	M	Sulur	Labourer	Roger	50	4	5	312	18	48	Yes	4	E	Respiratory failure
35	51626	Deepak	3.2.15	36	M	Kuniamuttur	Labourer	Malathion	25	3	4	1299	18	48	Yes	15	S	
36	52464	Vijayakumar	10.2.15	38	M	Selvapuram	Labourer	Roger	15	2	4	3456	12	48	Yes	15	S	
37	52439	Viji	10.2.15	45	M	Thondamuthur	Labourer	Diazinon	20	4	1	4356	6	48	No	8	S	
38	52536	Selvi	24.2.15	32	F	Pollachi	Housewife	Malathion	20	5	4	3245	18	48	Yes	14	S	

39	53241	Palanisamy	24.2.15	48	M	Dharapuram	Farmer	TIK-20	20	4	4	356	18	48	Yes	10	S	
40	54155	Karuppusamy	24.2.15	47	M	Dharapuram	Farmer	Monocrotophos	80	5	7	482	24		Yes	1	E	Respiratory failure
41	54175	Shankaran	3.3.15	35	M	Sulur	Labourer	Roger	50	3	6	134	18	48	Yes	6	E	Respiratory failure
42	53949	Vinoth	3.3.15	28	M	Thudiyalur	Labourer	Diazinon	75	4	7	116	24		Yes	1	E	Respiratory failure
43	54214	Anandkumar	3.3.15	25	M	Palladam	Farmer	Endosulphan	40	4	6	101	18	48	Yes	7	E	Respiratory failure
44	54568	Vijayalakshmi	16.3.15	17	F	Sultanpudur	Student	Monocrotophos	25	2	2	3445	12	48	Yes	12	S	
45	54997	Sathya	16.3.15	30	F	Ramanathapuram	Housewife	TIK-20	25	1	3	103	18	48	Yes	15	S	
46	55009	Gopalan	17.3.15	35	M	Annur	Farmer	Malathion	10	2	3	3664	6	48	No	10	S	
47	55041	Gowri	5.5.15	18	F	Tiruppur	Student	Monocrotophos	60	6	9	128	24		Yes	1	E	Respiratory failure
48	55084	Annapurani	12.5.15	26	F	Perur	Housewife	Roger	30	3	6	298	12	48	Yes	12	S	
49	56416	Priya	19.5.15	32	F	Ooty	Housewife	Parathion	50	4	7	325	18	48	Yes	5	E	Respiratory failure
50	56549	Venugopal	19.5.15	54	M	Ramanathapuram	Labourer	Monocrotophos	20	2	5	1860	18	48	Yes	11	S	