Recent Advances in Organophosphorus poisoning

A Chemical which can wipeout the Globe

Dr P. Narasimha Reddy MD;DA;

A short history

- 1854-Clermont developed OPC .
- 1935-Germans with Schrader prepared chemical warfare .
- 1956-PAM clinically used .
- A 100 year lag to develop treatment .

- OPC is a neglected child of toxicology research .

Global Burden

- Striking exposure and case fatality differences between developed and developing nations

- China,India,SriLanka,South America, Africa

- 30 lakh exposure
- 3 lakh deaths

United States
8000 exposure
<15 deaths

OPC case fatalities 10 to 50 %
Pharmaceuticals have <0.5%

- In India : 90% case fatalities occur in 20-40 yr group
  Rural and semi-urban
  Lower socio-economic class

Examples of organophosphates include:

- Insecticides
- malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion

- Nerve gases
- soman, sarin, tabun, VX

- Ophthalmic agents
- echothiophate, isoflurophate

- Antihelmintics
- trichlorfon.

- Herbicides
-
- tribufos [DEF], merphos) are tricresyl phosphate–containing industrial chemicals.

Source

Agriculture pesticide

Insect Baits

Pet shampoo

Surface sprays

Chemical Weapon

Conventional Classification based on LD-50

Extremely Toxic	Highly Toxic	Moderately Toxic	Slightly Toxic
1-50 mg/kg	51-500 mg/kg	501-5000 mg/kg	> 5000 mg/kg

- This classification is no longer of clinical value since even slightly .
- Toxic compounds can kill humans.
- Some mammals with high hydrolyzing enzymes survive less toxic OPC's .

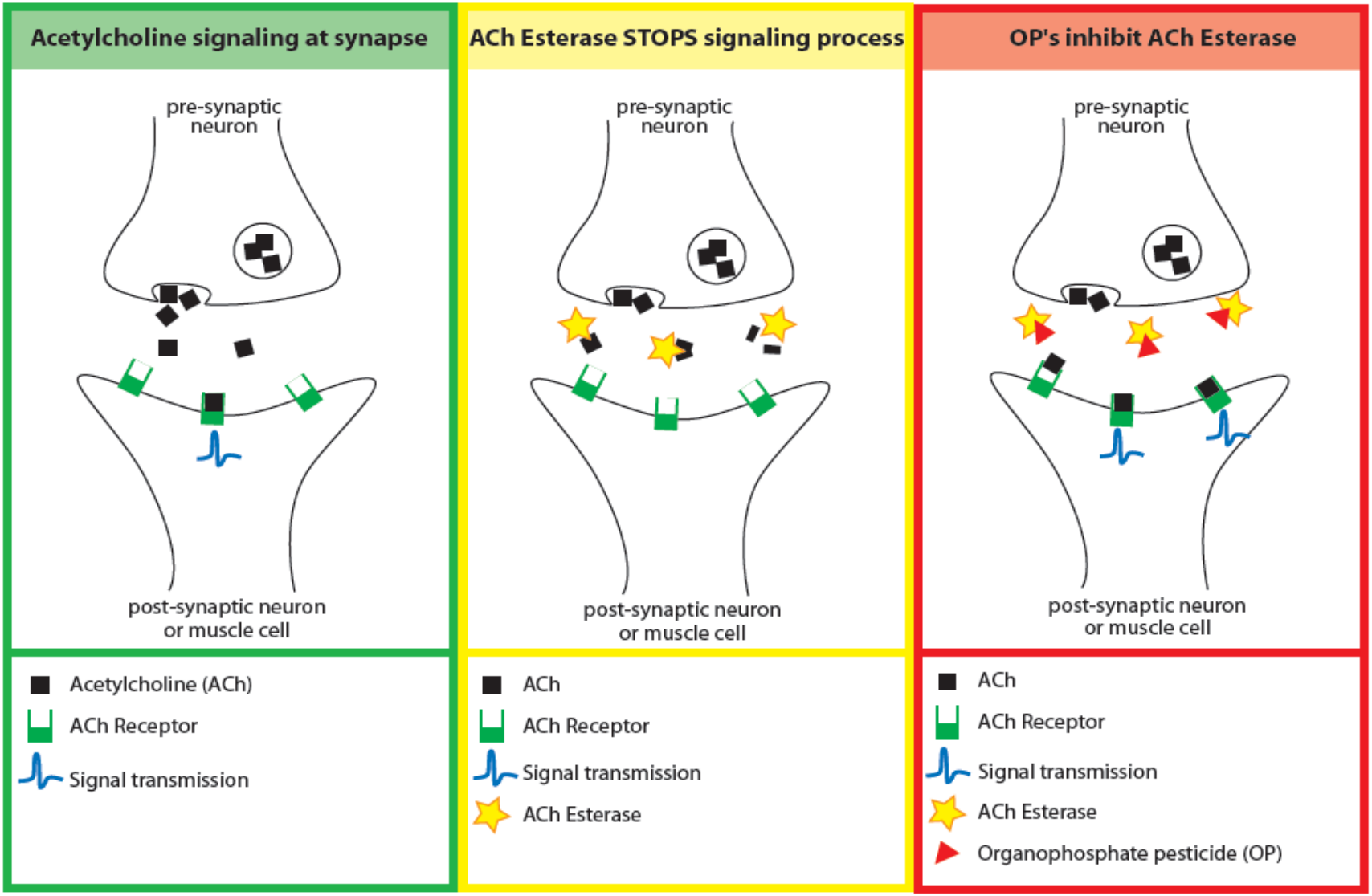
Organophosphates can be absorbed

- cutaneously,
- ingested,
- inhaled, or
- injected.

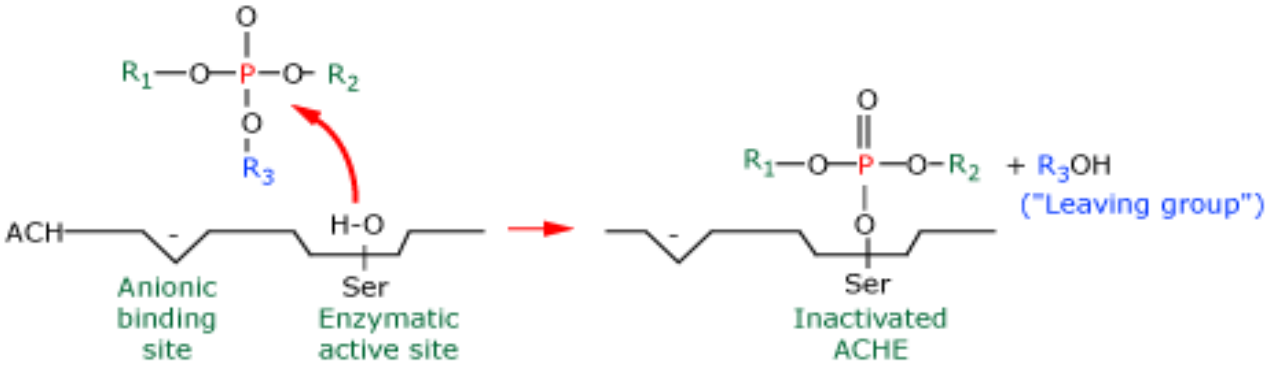
Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound,

- amount,
- route of exposure, and
- rate of metabolic degradation

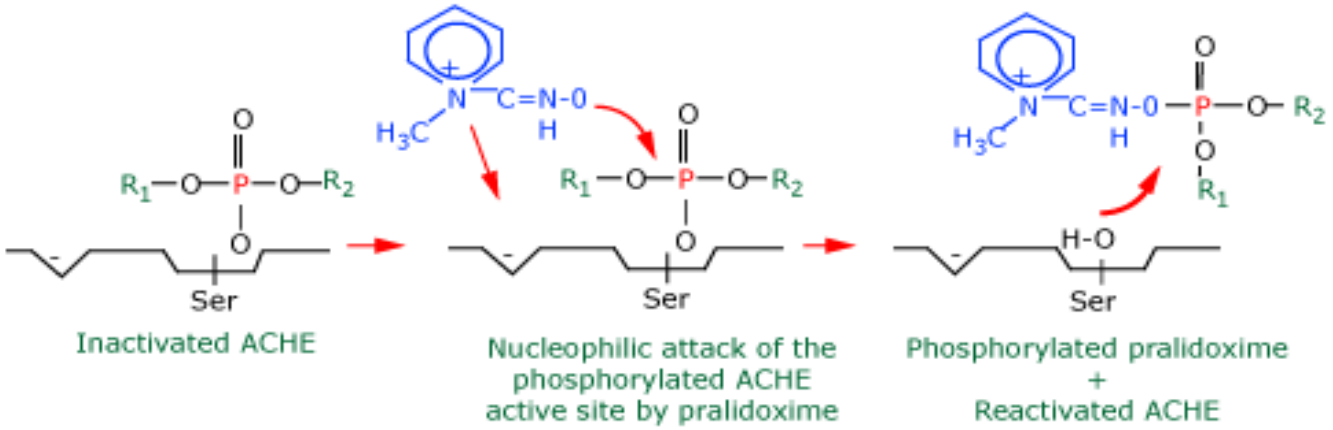
Mechanism of Toxicity


Acetylcholine signaling at synapse
pre-synaptic neuron
post-synaptic neuron or muscle cell
Acetylcholine (ACh)
ACh Receptor
Signal transmission
ACh Esterase STOPS signaling process
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ACh Esterase
OP's inhibit ACh Esterase
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ACh Esterase
Organophosphate pesticide (OP)

Mechanism of action: Organophosphate and pralidoxime

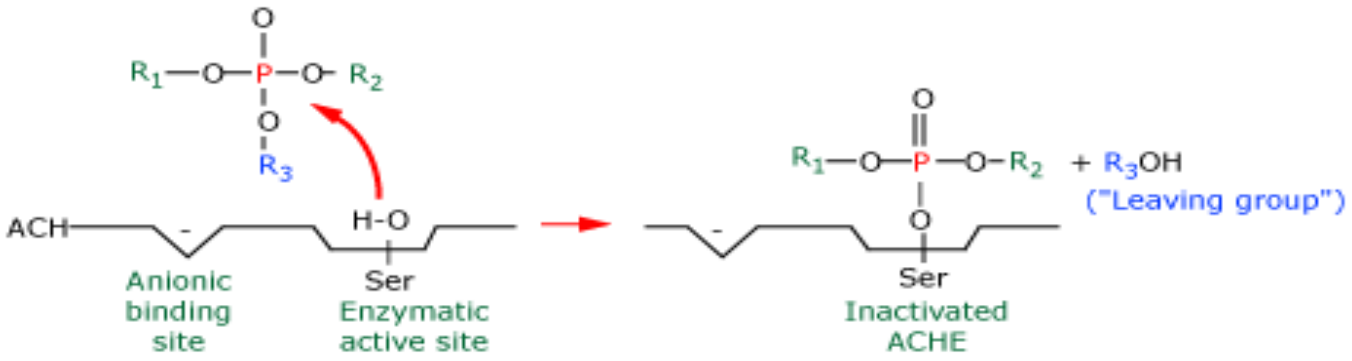


Acetylcholinesterase (ACHE) inhibition by an organophosphorone agent



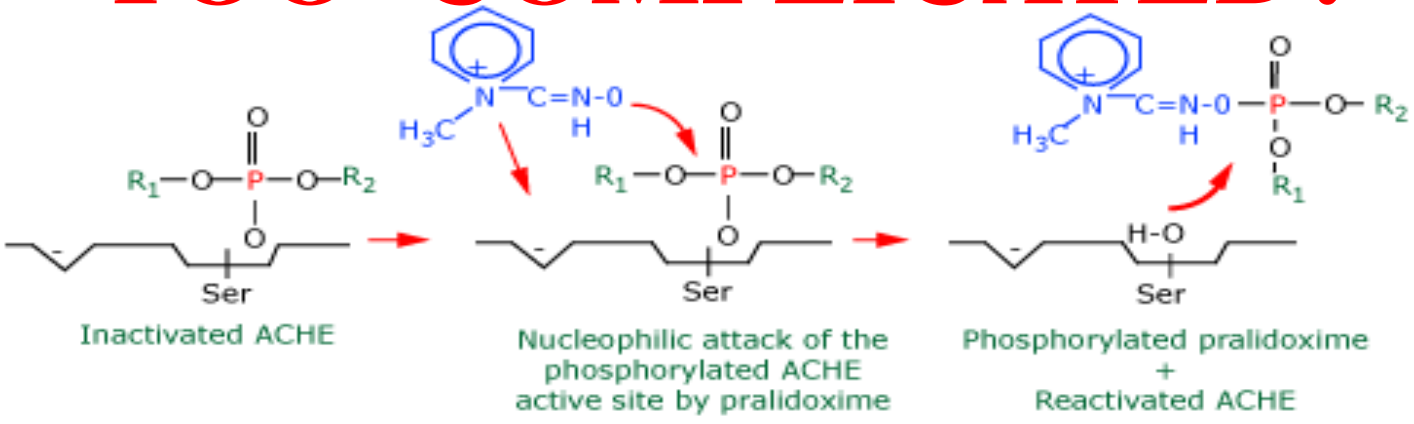
Reactivation of ACHE by pralidoxime

Mechanism of action: Organophosphate and pralidoxime



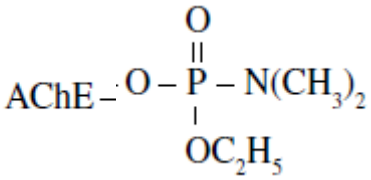
Acetylcholinesterase (ACHE) inhibition by an organophosphorone agent

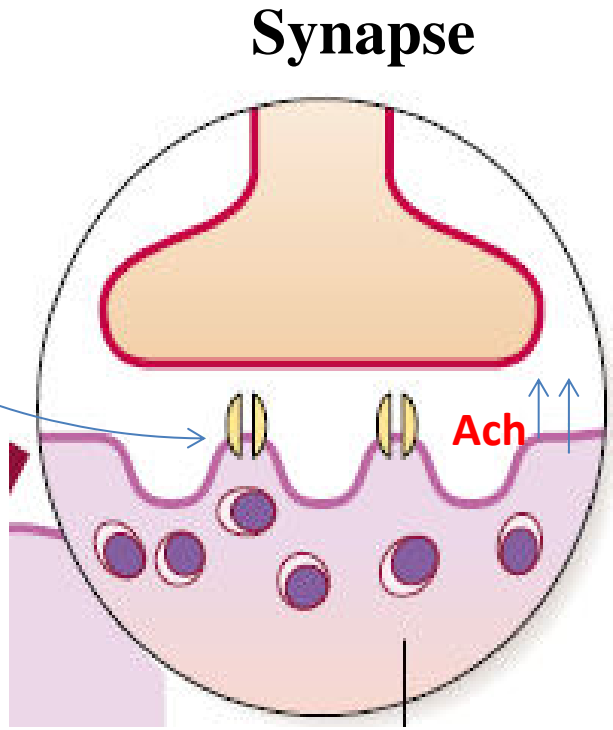
TOO COMPLICATED?



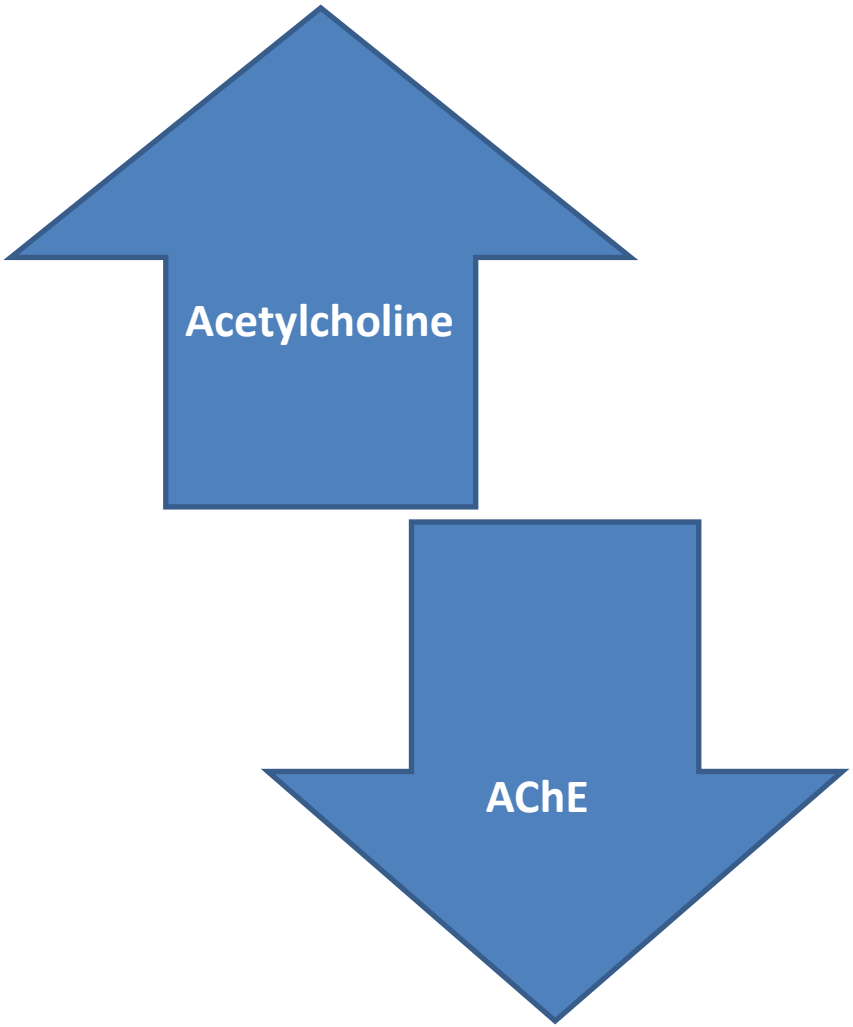
Reactivation of ACHE by pralidoxime

AChE-OPC complex





Consequences



Muscarinic sites	**Glands, Smooth muscles, Heart**
Nicotinic sites	NMJ, Autonomic ganglia, CNS

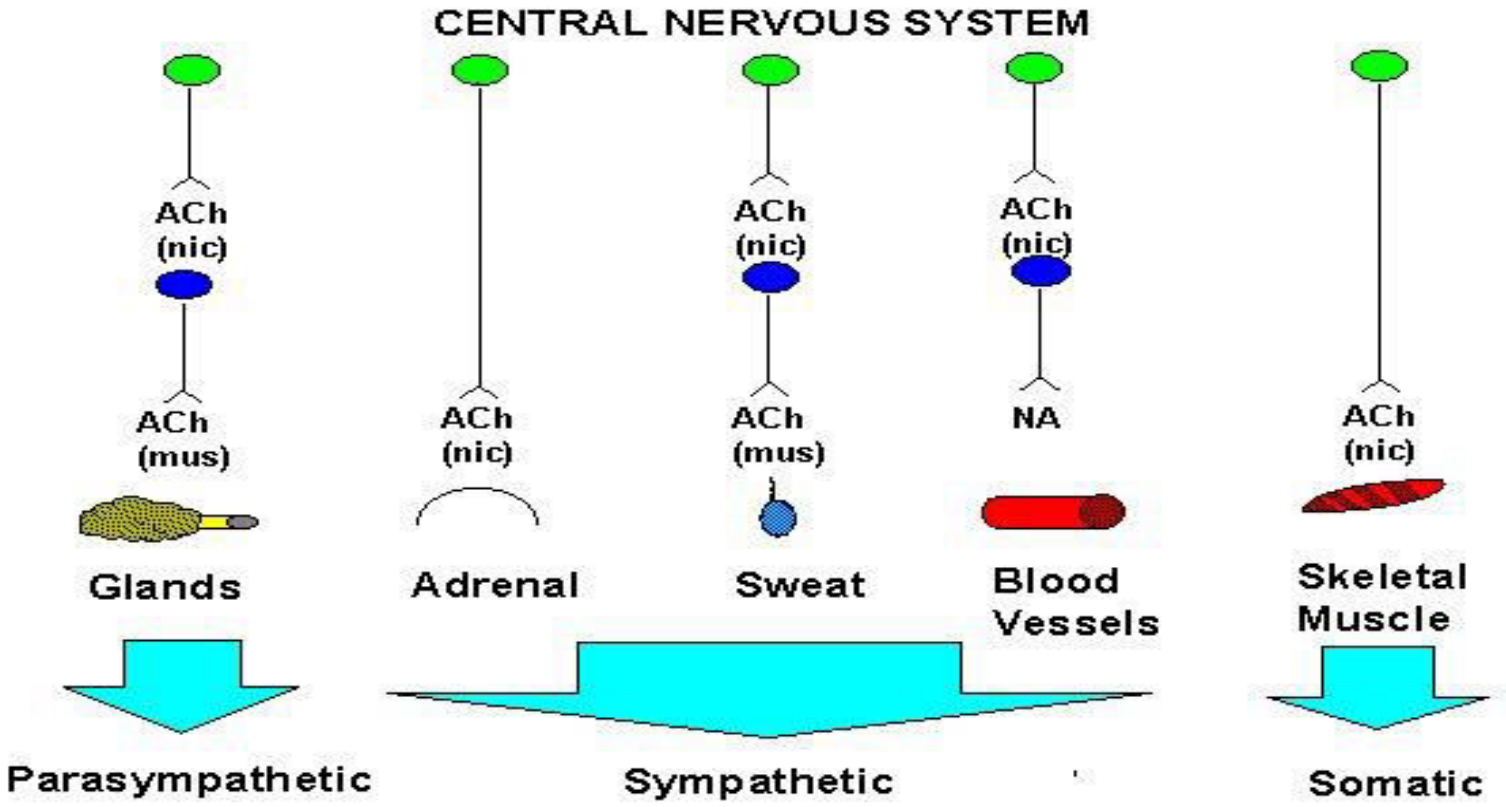
Cholinergic Crisis

Released from OPC in 48 hrs with Carbamates

Permanently destroyed- Aging

New enzyme regenerates

Clinical effects poisoning results from muscarinic, nicotinic, central nervous system.



OPC beyond cholinergic crisis

OPC beyond cholinergic crisis

- Direct Neurotoxicity
- Na Channel mediated
- Affects Astrocytes

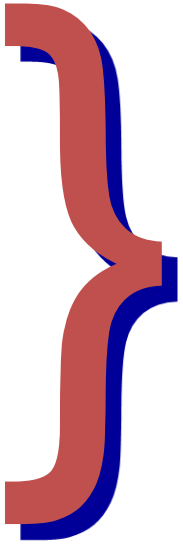
Direct Cardiotoxicity.
Na channel Mediated.
Occurs very early.

- Muscarinic brain receptor effects
- Unclear if Class specific

Dichlorvos related early death.

Clinical Features

- Acute Cholinergic Syndrome:
  - Central
  - Peripheral Muscarinic
  - Peripheral Nicotinic



Respiratory failure

+ Death

- Intermediate Syndrome
- OPIDN: Delayed peripheral neuropathy
- Neurocognitive dysfunction

Cholinergic Effects – "DUMBELS"

- D iarrhoea
- U rination
- M iosis
- B radycardia, Bronchorrhoea, Bronchospasm
- E mesis
- L acrimation
- S alivation

Contd….

- SLUDGE
- salivation,
- lacrimation,
- urination,
- diarrhea,
- GI upset,
- emesis

Nicotinic Effects

- **Muscle Weakness**
- **Respiratory difficulty**
  - diaphragmatic weakness
  - ***respiratory arrest***
- **Stimulation of sympathetic nervous system**

CNS effects

- Serious Effects
  - Coma
  - Respiratory centre depression
  - Seizures
- Other effects
  - Confusion
  - Memory loss
  - Disorientation
  - Delirium

Intermediate Syndrome

- Delayed Respiratory Failure
  - Proximal muscle weakness and CN lesions
  - Typically 1-4 days after cholinergic crisis has resolved
- Prolonged Effects on Nicotinic receptors
- Primary motor end plate degeneration
- Clinical importance
  - Delayed respiratory failure leads to death if not aware of it or prepared for it
    - *Wadia et. al 1974 : "Type II Paralysis, Senanayake and Karalliedde 1987"*

Chronic Effects

- **Organophosphate induced delayed neuropathy (OPIDN)**
  - 1-3weeks
  - Peripheral neuropathy
  - Axonopathy due to Neuropathy Target Esterases (NTE)
- **Chronic organophosphate induced neuropsychiatric disorder (COPIND)**

Difference in OPs - Toxicity

- **3 most common OP's** ingested are
  - Chlorpyrifos (**Diethly OP**)
  - Dimethoate & Fenthion (**Dimethly OP**)
- **Higher case fatality** and **intubation rates**
  - in Dimethoate (CFR 23%, Intu 35%) and Fenthion (CFR 16%, Intu 31%)
  - compared with Chlorpyrifos (CFR 8%, Intu 15%)

5 point assessment method

Eyes
Miosis

Skin
Profuse
Sweating

Lungs
Bronchorea
Bronchospasm

Pulse
Bradycardia

BP
Hypotension

Diagnosis

- It is a clinical diagnosis confirmed by estimation of choline esterase activity.
- RBC cholinesterase correlates well with CNS .
- AchE is the useful marker of OPC poisoning

- Other lab findings include
- leucocytosis, Haemoconcentration,
- metabolic acidosis , hyperglycemia , hypokalemia , hypomagnesaemia ,
- elevated troponin levels, amylase levels and elevated liver function tests.

Acetylcholinesterase Assays

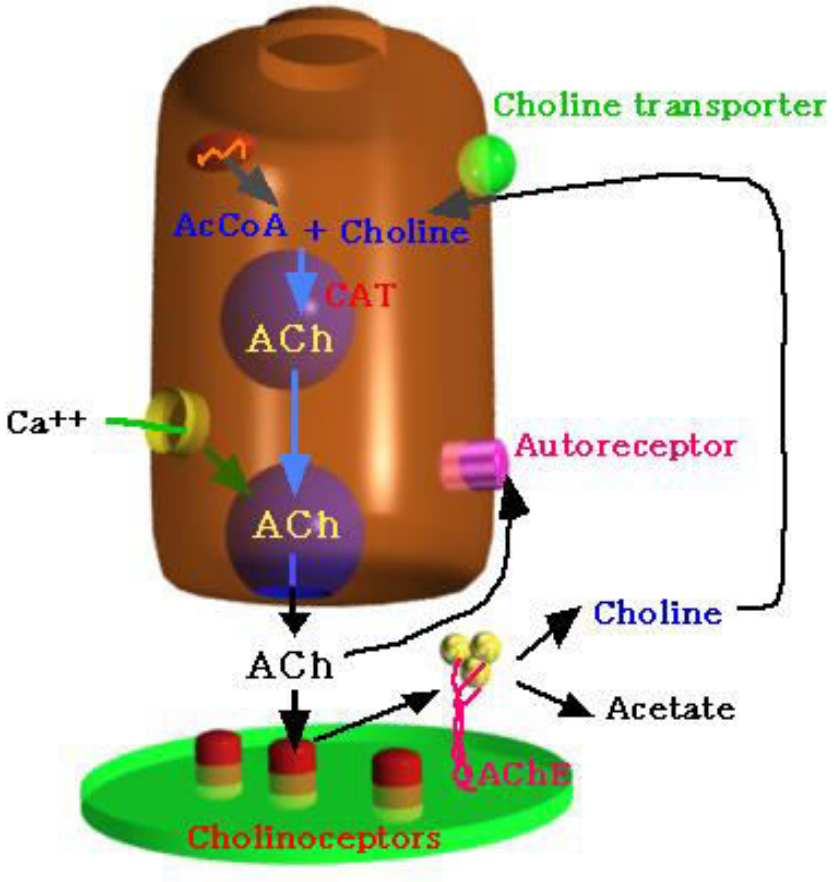
- Biomarkers of Exposure to Organophosphorus insecticide
  - Plasma cholinesterase(PChE)
    - Sensetive but Not specific
  - Red cell acetylcholinestersase (RBC-AChE)
    - Correlates better with AChE at synapse
- Different levels of inhibition with different OP agents
  - Chlorpyrifos vs Dimethoate
- Uses
  - Confirmation of diagnosis
  - Severity

Testmate ChE

- Designed for occupational exposure
- Quantitative test
- RBC-AChE and PChE
- Ellman method
- 4 minutes

Alternate sites for antidotes

- Protect AChE
- Supply AChE
- Reduce ACh
- Protect ACh Receptor
- Reduce OP Load
- Multiple Mechanisms



Management

The priorities in management are :

- **Resuscitation!**
  - A,B,C,D,E
- **Atropinisation** of symptomatic patients
- Decontamination
- Other Treatments – Oximes and others.

Resuscitation of OP poisoned patients

- **ABCDE** – Careful attention to management of *"airway + breathing"*
- **ATROPINE** is part of A, B, and C and
  - administer simultaneously to resuscitation
- GI Decontamination is **NOT** a life saving procedure!
  - Should not be performed before resuscitation

Respiratory Failure in OP patients

- Review of 376 OP poisoned patients ,90pts (24%) required intubation
  - 52 (58%) intubated within 2 hours
  - 46 (51%) died
  - 29 (32%) Well on admission but required intubation >24hrs

[1]Eddleston M, Mohamed F, Davies JO, Eyer P, Worek F, Sheriff MH et al. Respiratory failure in acute organophosphorus pesticide self-poisoning. QJM. 2006;99(8):513-22.

Atropine administration in OP poisoning

- Indications
- How fast to give
- For how long
- Toxicity of Atropine

Indications for Atropine and Speed of intial Atropinisation

Indications

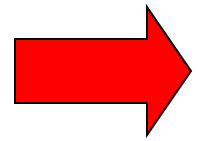
Poor air entry in lungs caused bronchospasm and bronchorrhoea

Hypotension

Bradycardia

Excessive sweating

(Miosis)



Atropine

Atropinisation – Endpoint

Chest Clear

Systolic BP >80mmHg

Heart rate >80/min

Dry Axillae

Pupils no longer pinpoint

Speed of intial Atropinisation

- Study looked at severely poisoned OP patients in Sri Lanka
  - 22 patients, all required intubation, but survived to discharge
  - Mean dose of atropine required 23.4mg (range 1-75mg)

Eddleston et al. Speed of initial atropinisation in significant organophosphorus pesticide poisoning--a systematic comparison of recommended regimens. J.Toxicol.Clin.Toxicol. 2004;42(6):865-75.

- Text book recommendations for atropinisation varied markedly
  - Average patient 23.4mg – (8 to 1380 mins)
  - Severely ill patient 75mg – (25 to 4440 mins)

Suggested Atropine Regimen

- Loading
  - Doubling dose regime e.g. 2 4 8 16 mgs every 5 minutes
- Maintenance
  - Continuous infusion < 3mg/hr
  - 10-20% of loading dose/hour
- Endpoints
  - Clear chest on auscultation with no wheeze
  - Heart rate >80 beats/min

What if you give too much Atropine ?

- Anticholinergic Syndrome:
  - Hot as hell
  - Blind as a bat
  - Red as a beet
  - Dry as a bone
  - Mad as a hatter

CVS - Severe Tachycardia (eg HR >120)

Risk of ischaemia in elderly patients

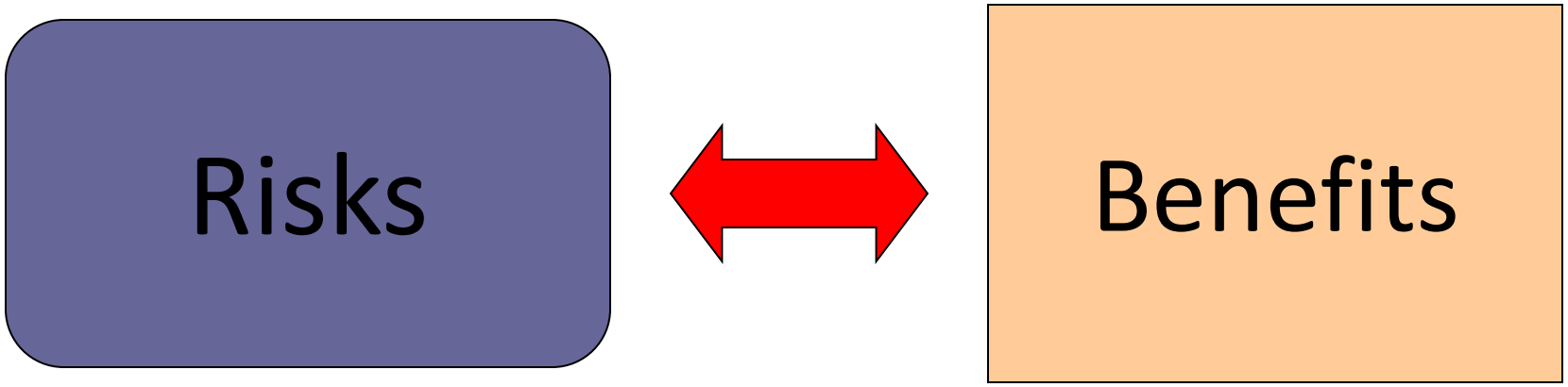
CNS - Confusion, Agitation

Hyperthemia

Gastrointestinal Decontamination

?

Gastrointestinal Decontamination



- **Aspiration**
- **Trauma**
- **Electrolyte Imbalances**
- **Cardiac Arrest**
- **Cost**

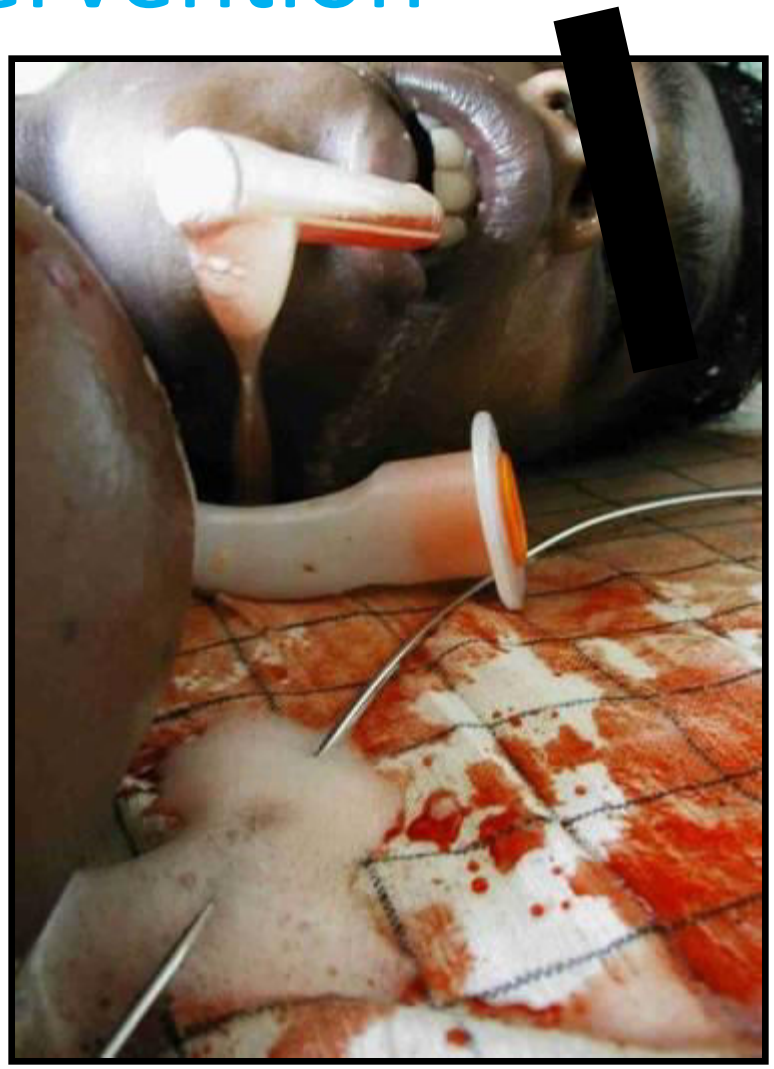
- **Removal of poison load**
- **Prevention of ongoing poison absorption**
- **More beneficial in Toxic OP's**

Gastrointestinal Decontamination Options:

- Nothing
- Emesis
- Gastric Lavage
- Activated Charcoal

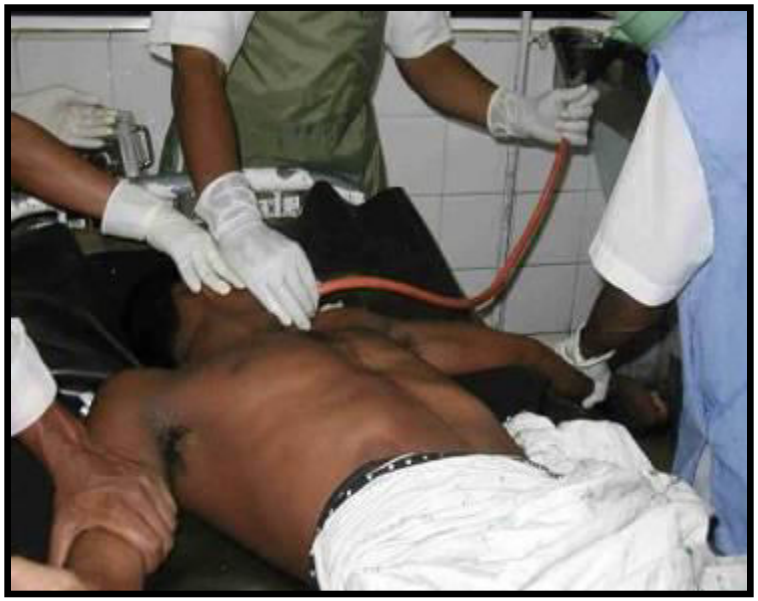
Risk of Intervention

- Aspiration
- Trauma
  - Oesphageal Injury
  - Nasopharyngeal injury



1. Eddleston M, Haggalla S, Reginald K, Sudarshan K, Senthilkumaran M, Karalliedde L, et al. The hazards of gastric lavage for intentional self-poisoning in a resource poor location. *Clin Toxicol (Phila)* 2007;45(2):136-43.

Risk of Intervention



- Electrolyte Abnormalities
- Cardiac Arrest
  - Increased **Vagal Tone** especially with toxin induced bradycardia
    - Induced emesis, Lavage
- Cost

Summary of Experimental Evidence

- GI decontamination should be done in ideal settings
  - Means to **protect airway**
  - Expertise to carry out procedure safely

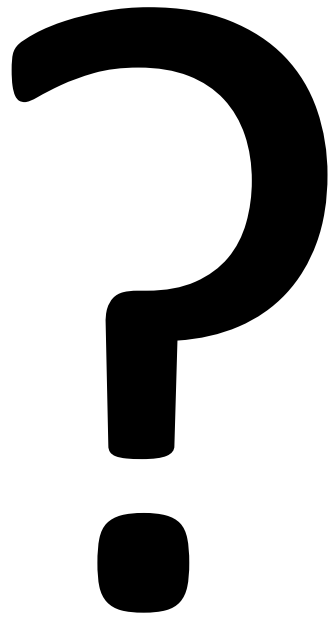
- Little benefit in outcomes after 1 hour

  - Position statement: single-dose activated charcoal. *J Toxicol Clin Toxicol* 1997;**35:**721-41.
  - Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999;**37:**731-51.

Decontamination for OPs

- Within 1 hour
  - Gastric lavage if no contraindications
    - Able to protect airway
    - GCS >12
  - Followed by single dose AC
- 1-2 hours – debatable
  - In some centres the above treatment is acceptable
- > 2 hours ingestion
  - No place for Gastric Lavage or AC

Oximes



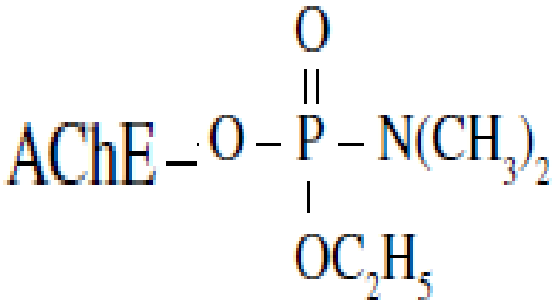
Oximes in OPC poisoning.

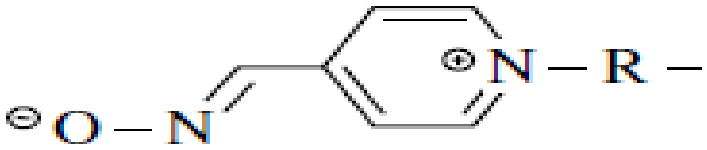
Pralidoxime,Obiodoxime

HI-6,Hlo-7

K-oximes, sugar oximes

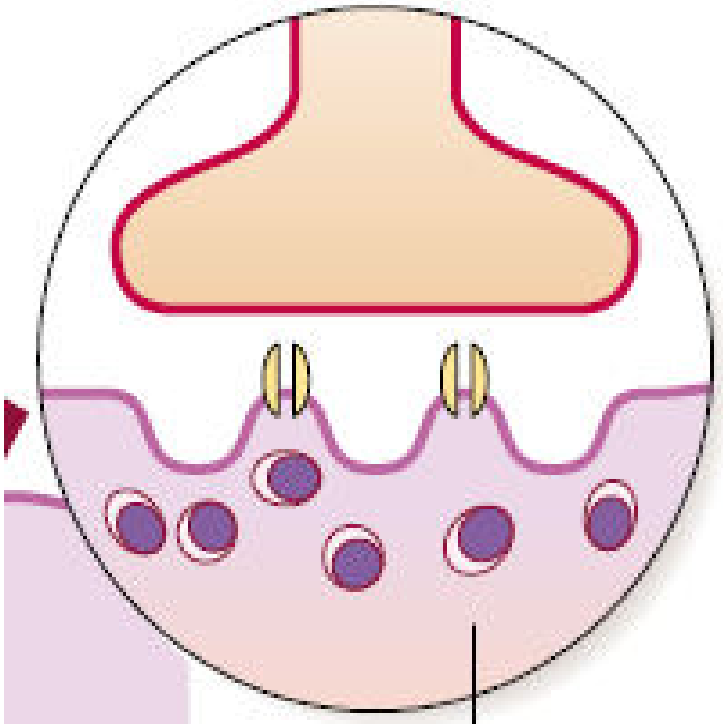
AChE-OPC complex

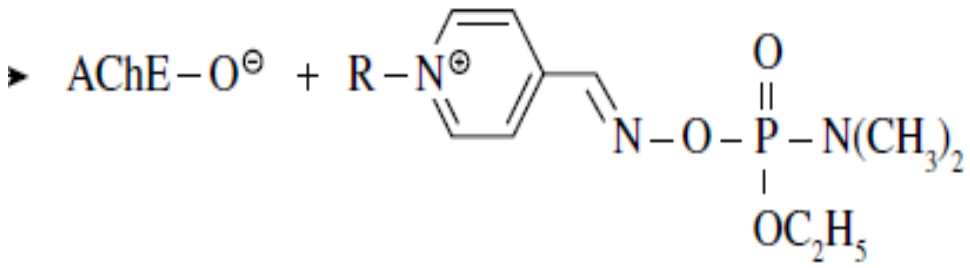




Reactivator

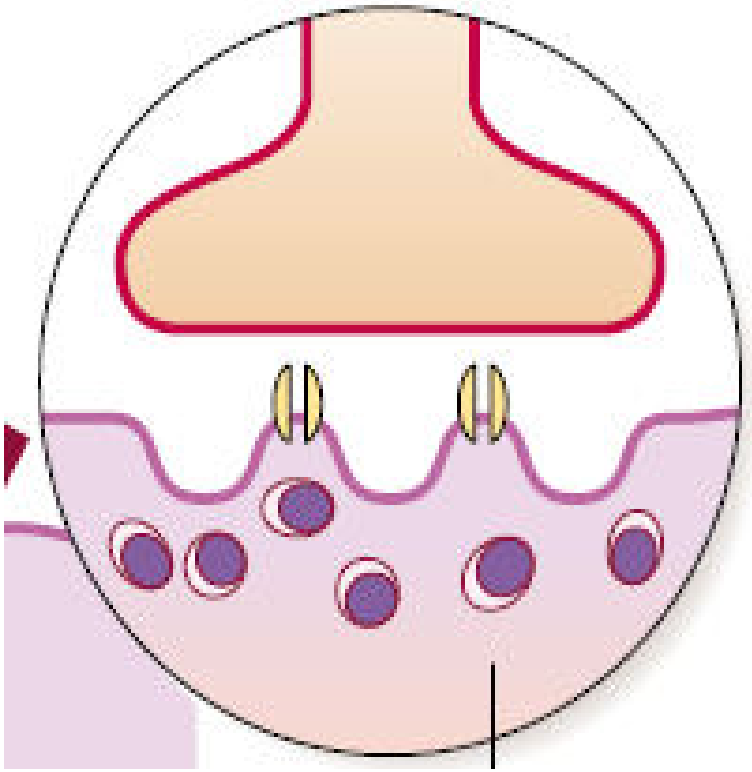
Synapse





Liberated enzyme Phosphorylated oxime

Synapse



Past to present of Pralidoxime

Samuel et al , 1995	N=72, 1g loading vs. 12g infusion over 4 dys . ↑ Mortality (22% Vs 14%) with PAM use. Atropinization details inadequate, no placebo group .
Cherian et al, 1997	N=110 , 12 g PAM over 3 days Vs Placebo. ↑ Mortality (29% Vs 5%) with PAM . Atropinization details inadequate .

Past to present of Pralidoxime

Pawar et al. 2006

N=200, 2g loading followed by either low dose 6g/day or high dose 1g/hour for 48 hr then 6g/day .

↓ Mortality in high dose group (1% Vs 8%) .

↓ need for intubation in high dose group (64% Vs 88%).

Used iodide preparation, did not use WHO protocol .

Eddelson et al. 2009

N=235, followed WHO protocol which is 30 mg/kg load Over 20 minutes followed by 8-10 mg /kg/hr till 24 hour atropine **is stopped or for 7 days (whichever is longer).**

Non-significant ↑ death with PAM (24.8% Vs 15.8%) .

Shorter duration of ventilator days with PAM (2 Vs 6.5 dys) .

Early indicators that PAM may be more useful in Di-ethyl OPC

Newer oximes

K-27,K-48 ,K-75 , sugar oximes
RR of death decreased by 19%
Reactivation rate > 10 %
Can be combined
Can cross BBB

Barelli et al. Minerva Anaesthesiol 2011:77:1197-1203

Newer strategies

Prevent NMJ failure

Neuromuscular nAChR antagonist
Prevents fasciculation and muscle weakness

Synthetic carboxyl esterases which hydrolyse OPC

Low dose pancuronium can decrease supra-maximal maximal nerve stimulation .

Improve compound muscle action potential

Oxygenation in OP poisoned patient
How important is it?

Oxygenation in OP poisoned patient

Box 1. Quotes from articles stating the need for oxygen prior to atropine in OP pesticide poisoning

'Atropine must not be given until oxygenation is adequate, or ventricular fibrillation may occur.'[30]

'Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation'[39,61]

'In order to obviate the added risk of hypoxia-induced ventricular dysrhythmias, correct cyanosis before administering atropine'[15]

'Adequate oxygenation is important as atropine can precipitate ventricular fibrillation in the presence of hypoxia'[19]

'Supplemental oxygen should be given, ideally before atropine administration, as hypoxia may increase the risk of atropine-induced dysrhythmias'[34]

Oxygenation in OP poisoned patient

Is oxygen required before atropine administration in organophosphorus or carbamate pesticide poisoning? – A cohort study

L. A. KONICKX,[1,2] K. BINGHAM,[1] and M. EDDLESTON[1,3]

Clinical Toxicology (2014), **52**, 531–537

- Only 4 of 1957(0.2%) patients developed fatal arrythymia.
- Recommend not to defer atropine if oxygen not available.

Recent UPDATES

- Mild to moderate **alkalinization** is effective.
- Gacyclidine; **an antiglutamatergic** compound, was beneficial in conjunction with atropine, pralidoxime, and diazepam .
- **I.V MgSO4** decreased hospitalization duration and improved outcomes in patients with OPC poisoning.
- Bio-scavengers including FFP (or) albumin recently been suggested as a useful therapy.

Gacyclidine

- **CNS toxic effects results from increased excitory release of glutamate .**
- **An antiglutamatergic compound** .
- Beneficial in conjunction with atropine, pralidoxime, and diazepam in nerve agents poisoning.
- Gacyclidine inhibited the neuropathology that occurred three weeks following soman exposure in animals.

Sodium Bicarbonate

- Moderate alkalinization (pH between 7.45 and 7.55).

- Sodium bicarbonate was first used to correct the metabolic acidosis.

- Regarding its enhanced therapeutic effects, the infusion of higher doses of sodium bicarbonate (5 mEq/kg in 60 min followed by 5-6 mEq/kg/day) was shown to be useful.

Magnesium Sulphate

- Intravenous magnesium sulfate (4 g) given in the first day after admission.
- Decrease hospitalization period and improve outcomes in patients with OP poisoning.
- Blocks calcium channels and thus reduce ACH release.
- Reduced CNS overstimulation & reversed the neuroelectrophysiological defects.

- Clonidine
  - Decrease the presynaptic synthesis and release of acetylcholine.
  - Central nervous system > peripheral cholinergic synapses
- Diazepam
  - Diazepam reduces respiratory failure (rats) and cognitive deficit (primates)
  - Postulate “uncoordinated stimulation of the respiratory centres decreases phrenic nerve output”.

Adrenergic Agonists

- Clonidine reduces acetylcholine synthesis.

- On humans not proven.

Antioxidants

- OP Compounds:
  - Induce reactive oxygen radicals.
  - decreases total antioxidant capacity, and increases thiobarbituric reactive substances and lipid peroxidation.

Bio-scavengers

- Fresh frozen plasma (FFP) or albumin has been recently suggested as a useful therapy through clearing of free organophosphates.

- FFP increases ChE levels and prevent the intermediate syndrome.

Beneficial in animal studies

- Neuroprotection via anticholinergic and antiglutamatergic agents...

  -Huperzine A, is a reversible ChE inhibitor with imidazenil, 1 is a GABA A receptor modulator .

  - In post-exposure treatment, prevent seizures and status epilepticus.

- Anti-muscarinic drugs with antiglutamatergic properties:

  -Aprophen, benactizyne and caramiphen

Cont…….

- Ketamine, a noncompetitive NMDA receptor antagonist

can be used in nerve agent-induced seizures specially, when administered in combination with midazolam or diazepam.

- Tezampanel, another glutamate receptor antagonist, which is specific for kainate sub-type receptors, was reported to be useful against soman-induced seizures.

Cont…….

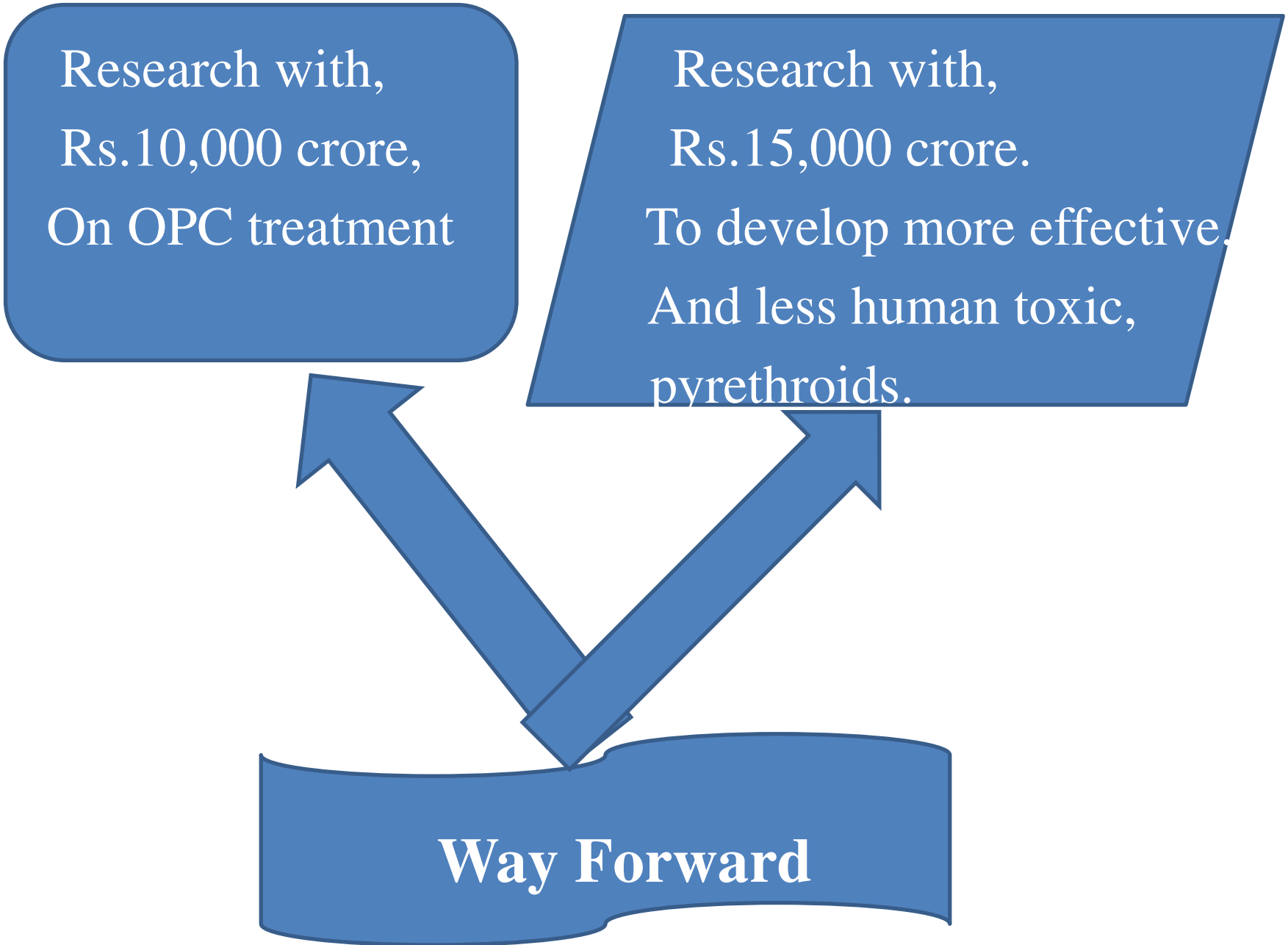
- **Hemofiltration and antioxidants are also suggested**.

- **Recombinant bacterial phosphotriesterases and hydrolases** that are able to transfer organophosphorous-degrading enzymes are very promising in delayed treatment of OPC poisoning.

- Recently, encapsulation of drugs or enzymes in nanocarriers has also been proposed.

Cont……

- **Contraindications:** - Drugs like morphine, succinylcholine, theophylline, phenothiazine and reserpine.


Research with,
Rs.10,000 crore,
On OPC treatment
Research with,
Rs.15,000 crore.
To develop more effective.
And less human toxic,
pyrethroids.
Way Forward


THANQ