

# DM SEMINAR

## August 18, 2006

Organophosphate poisoning: current management strategies.

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# Organophosphate poisoning: Magnitude of problem.

WHO estimates acute pesticide poisonings at 3 million cases/ year.

1 million accidental & 2 million suicidal; likely underestimate

300,000 deaths/ year

>99% occur in the developing world.

Organophosphate agents commonly used as pesticides.

These agents responsible for over 70% of the cases in most of South Asia.

Most deaths may occur at home, small towns. Hospital statistics gross underestimate

Four fold increase in mortality in the last years.

Senananayake. Hum Exp Toxicol 1995; 14: 808-811  
Eddleston M. Self poisoning with pesticides. BMJ 2004, **328:42-44**

The case fatality for self-poisoning in the developing world is commonly 10–20%,

For particular pesticides it may be as high as 50–70%

Contrasts with the less than 0.3% case fatality ratio normally found for self-poisoning from all causes in Western countries.

The causes of the high case fatality are multifactorial

1. the high toxicity of locally available poisons,
2. difficulties in transporting patients across long distances to hospital,
3. the paucity of health care workers compared with the large numbers of patients, and
4. the lack of facilities, antidotes, and training for the management of pesticide-poisoned patients

A large cohort of 10,000 cases of OP poisoning & carbamate ongoing in north central Sri Lanka

6000 already recruited to standardized protocol

# PGI emergency data .

15 year data 1990-2004  
Unpublished thesis data..

Ongoing retrospective study of number of poisoning admissions to PGIMER  
Emergency services.

Data reflective only of number requiring admissions. EMOPD excluded.

Bias toward organophosphate poisoning likely. Also might overestimate mortality data.

**Total number of poisonings admitted: 1420**

**Total number of organophosphate poisonings admitted: 557**

**Admission as percentage of total: 39.2%**

**Outcome Data available for 483 cases.**

**Number alive/discharged: 397( 82.2%)**

**Mortality: 86( 17.8%)**

# RICU Data.

Unpublished data  
Data collected as part of data analysis.

8 years data (1998-2005)

**1290** admissions.

Number of poisonings **admitted to RICU: 82**

Number of **organophosphate poisonings: 52(63%)**

**Number died: 8(15%)**

# Forensic autopsy data.

Journal of Clinical Forensic Medicine (2003) 10, 145–152

A 25 year (1977–2002) autopsy study of 5933 unnatural fatalities

Abrupt rise in unnatural deaths (3050; 51.4%) since 1997.

84.2% subjects were between the age group of 16 and 45

Accidental deaths (79.3%) constituted the majority of unnatural fatalities followed by suicidal (13.9%) and homicidal (6%) deaths.

Between 1977 and 1987, poisoning data.

**Barbiturates (33.3%)**

**Organophosphates (23.8%) and**

**Copper sulphate (14.3%)**

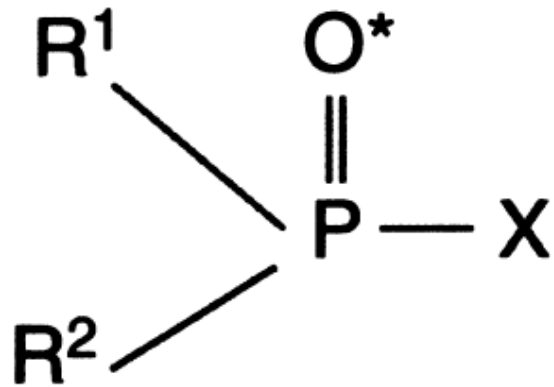
Between 1987–1997 data

**Organophosphates (45%) and**

**aluminium phosphide (26.5%)** were the major fatal poisons.

Since 1992 aluminium phosphide (80%), a fumigant pesticide used for wheat preservation was the most common poison.

General structural formula of an organophosphorus insecticide.



\*or S

In the most commonly used insecticides, R1 and R2 consist of either two-methyl or two-ethyl ester groups to form a dimethyl or diethyl phosphoryl insecticide, respectively.

# Classification of OP agents based on leaving group

## Group 1: Phosphorylcholines.

Substituted quaternary N

Echothiopate

## Group 2: fluorophosphates

fluoride

dimefox, sarin.

## Group 3: cyanophosphates/ halophosphates

CN, SCN, OCN

tabun.

## Group 4: multiple constituents

“R group”

dimethoxy

chlorothion, fenthion,  
malathion, temephos  
methylparathion  
dichlorvos.

diethoxy

chlorfenvinphos, ethion  
phorate, TEPP, diazinon,  
parathion, coumaphos

dialkoxy

isopropyl paraxoan

diamino

schradan

chlorinated/ subs dialkoxy

haloxan

trithioalkyl

merphos

triphenyl

TOCP



# Mode of poisoning.

Unintentional

Suicidal

Accidental:            agricultural workers  
                             children, adults-areas where “fogging” done

Homicidal.

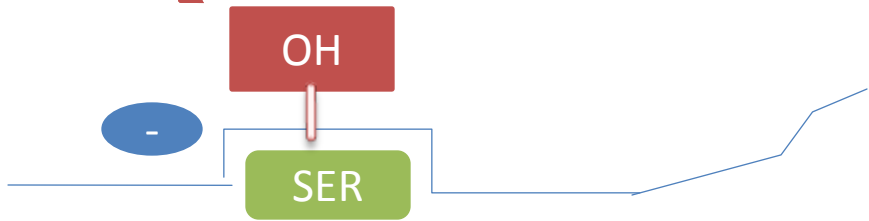
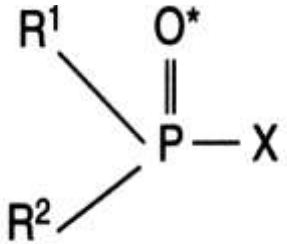
Mode of poisoning:

Often ingested: a) intentional b) accidental

Inhalation

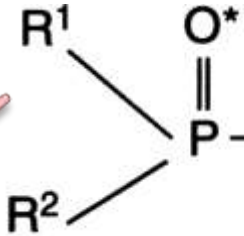
Dermal contact.

# Mechanism of Action of OP Poisoning.

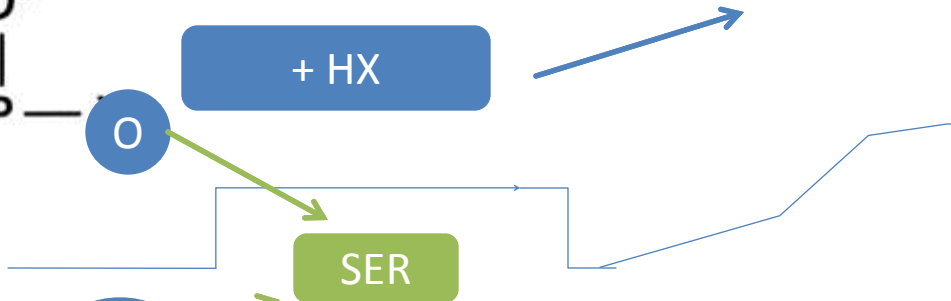
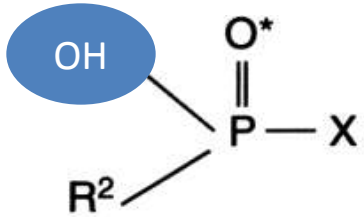


STEP 1

AGING

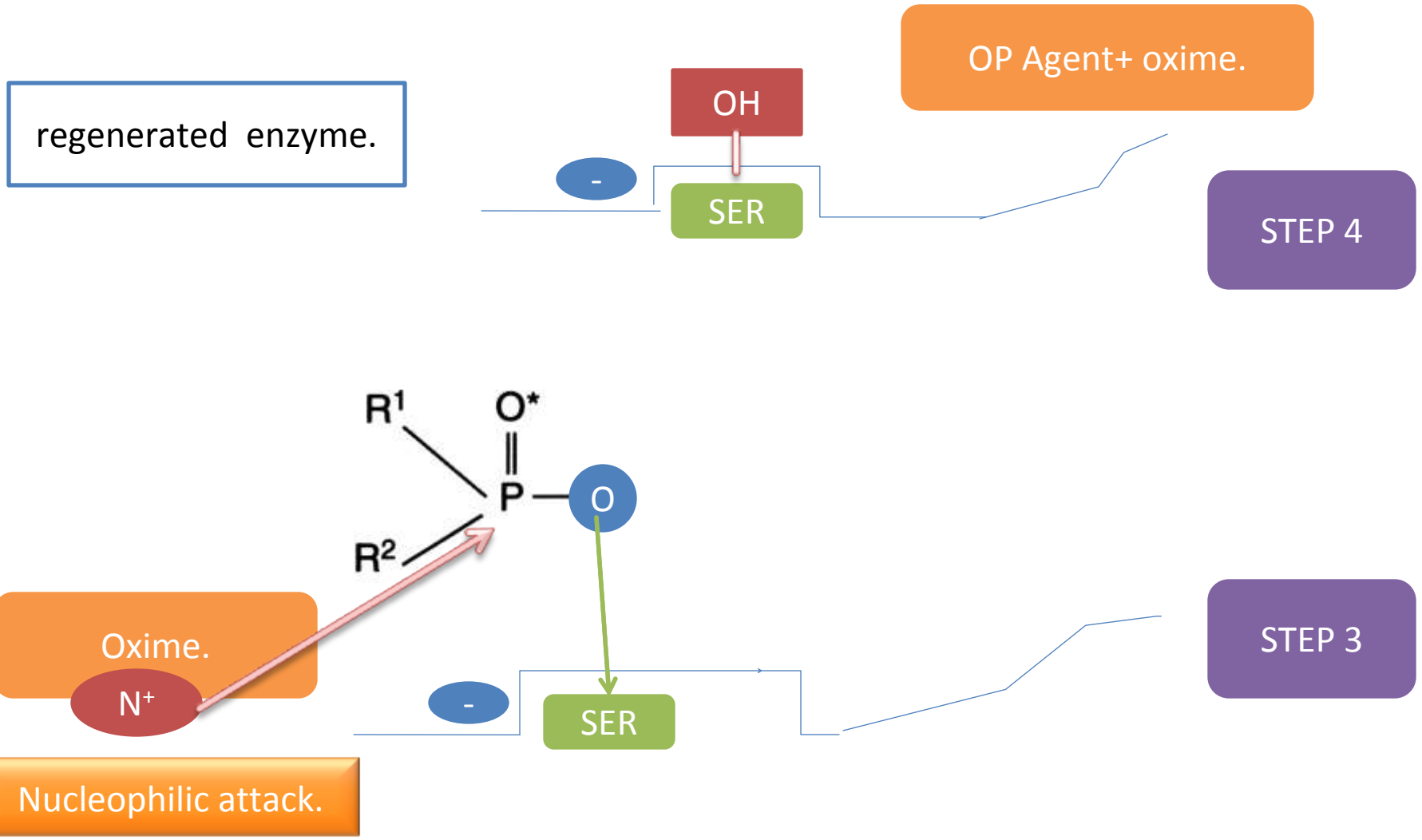


+ HX



STEP 2

# Mechanism of regeneration in OP Poisoning.



# Pharmacokinetics of OP poisons:

Well absorbed from lungs, gastro-intestinal tract, skin, mucous membranes, conjunctiva.

Most are lipophilic

Peak levels seen 6 hours after absorption.

Serum  $t_{1/2}$  minutes-hours.

Distribution into fat & salivary gland( esp chlorfenthion, fenthion) and CNS.

Fat re-distribution allows measurement of insecticide upto 48 hours.

Metabolized by mixed function oxidases in liver and intestinal mucosa.

Inhibit various carboxylic esterases like chymotrypsin, AchE, plasma cholinesterase, plasma and hepatic carboxylesterases (aliesterases), paroxonases ( A esterases) and other non-specific esterases.

# Clinical features of OP Poisoning.

Massive ingestions symptomatic < 5 minutes; usually < 8 hours & nearly all symptomatic < 24 hours.

Lipid soluble agents longer time to onset

## **MUSCARINIC action:**

**SLUD, DUMBBELS**

Miosis most consistent sign.

Both sympathetic & para- sympathetic over-activity.  
ganglionic stimulation masks cholinergic action.

Mydriasis in 15% of cases.

bronchodilatation, urinary retention.

hypoglycemia may occur

amylase may be raised

1.salivary amylase

2.pancreatitis sec sphincter Of Oddi dysfunction.

Transaminitis may occur.

**Cardiovascular manifestations:**

tachycardia, hypertension  
bradycardia, AV block  
prolonged QTc & torsades de pointes.

**Pulmonary manifestations:**

bronchorrhoea  
bronchospasm  
respiratory muscle weakness  
ALI/ARDS  
Aspiration pneumonitis( lipophilic agents)

**Nicotinic stimulation:**

initial fasciculation, weakness( *depolarization*)

paralysis of respiratory muscles

**CNS features:**

CNS depression  
agitation, delirium  
extra pyramidal effects

## Etiology of intermediate syndrome

The cause of the syndrome is a matter of considerable controversy.

The observed features are consistent with the following sequence

1. The prolonged presence of inhibitory oxon in the circulation of severely poisoned patients
2. Consequential persistent inhibition of AChE not reversed by (possibly inadequate) treatment with oxime
3. Prolonged nicotinic cholinergic stimulation causing functional paralysis of neuromuscular transmission.

May be caused by local necrotic damage at the motor end-plate and skeletal Muscle

Nowadays believed to be due to combined pre-synaptic & post-synaptic block.

# Intermediate syndrome vs delayed neuropathy.

Variable	Intermediate syndrome	Delayed neuropathy
Time of onset	1-4 days	2-3 weeks
Sites of weakness		
Limb weakness	Proximal	distal
Neck weakness	+	-
Cranial weakness	+	-
Respiratory muscles	+	-
EMG	Tetanic fade	Denervation
Recovery time	4-18 days	6-12 months
Agents implicated	fenthion Dimethodate Monocrotophos.	Methamidophos Trichlorphon leptophos



## **Organophosphate induced delayed polyneuropathy (OPIDN)**

OPIDN is common following exposure to OPCs which have weak anticholinesterase activity e.g. TOCP

Number of OPCs have been found to be neuropathic e.g. mipafox, merphos, leptophos, DEF,EPN, cyanophos and trichloronat.

OPIDN sets in after a period of 7-21 days of exposure and causes significant morbidity. The earliest symptoms to be seen are paraesthesiae and calf pain. Weakness initially appears initially in the distal leg muscles causing foot drop

The cranial nerves and the autonomic nervous system are not involved.

Sub acute in onset in contrast to other toxic axonopathies, with a slow progression over 2 weeks.

Clinical involvement of the corticospinal tracts and the dorsal columns becomes apparent when the peripheral neuropathy improves.

Phosphorylation and subsequent ageing of an enzyme in axons called as neuropathy target esterase. Deficit in severe cases is often permanent.

# Extra-pyramidal manifestations.

Increasingly recognized manifestation.

**Termed as “chronic organophosphate induced neuropsychiatric disorders” (COPIND).**

Due to inhibition of cholinergic neurons in the striatum( caudate & STN).

May be more with lipophilic agents like fenthion.

Davis et al in 1978 described EPS syndrome in chronic repetitive poisoning.

Davis KL, J Nerv Ment Dis 1978;166:222-5.

Commonest reported features in acute toxicity are oculogyric crisis and rigidity

Bhatt et al (1999) described typical Parkinson’s disease like manifestations

Bhatt MH, Elias MA, Mankodi AK. Acute and reversible parkinsonism due to organophosphate intoxication: five cases. Neurology 1999;52:1467.

Neuroleptic malignant syndrome described during recovery from acute OP poisoning

Onset **4-40 days.**

Disappear spontaneously **in 1-8 weeks**

Imaging usually normal.

One case report with Putaminal hyper-intensities

Rule out

**hypoxic-ischemic damage**  
**drug-related.**

Features described

Atypical ocular bobbing

Opsoclonus

Cerebellar ataxia

Choreoathetosis

Dystonia, tremor.

Psychiatric manifestations

Parkinsonism

# Peradeniya organophosphate poisoning score

Parameter	score
Miosis	
pupil > 2mm	0
pupil ≤ 2mm	1
pupil pin-point	2
Fasciculation	
none	0
present	1
generalized/ continuous & cyanosis	2
Respiration	
≤ 20/min	0
> 20/ min	1
> 20/ min & cyanosis.	2
Bradycardia	
> 60/ min	0
41-60/ min	1
≤40/ min	2
Level of consciousness	
conscious/ alert	0
impaired, responds to verbal commands	1
no response to verbal commands	2
convulsions.	+1
<b>Total</b>	<b>11</b>

# Assaying toxicity.

**Ideal test:** plasma insecticide levels  
urinary metabolites



1. Too short  $t_{1/2}$
2. too many compounds

Plasma cholinesterase values.

## **Pros.**

Falls rapidly after toxicity

Recovers rapidly

Easily assayed

## **Cons.**

Less specific

Affected by many disease states

Drug related changes

Increased in hypoalbuminemia

Day to day variation 20%

## RBC cholinesterase values.

RBC Cholinesterase more accurate reflector of tissue AchE inhibition.

Inhibition long-lasting.

Activity may take > 66 days to stop declining & > 120 to return to normal

Other disease states may spuriously reduce values

Falsely elevated by OCP's.

Genetic & circadian variation upto 10%

Not reliable < 4 months of age.

# Problems in cholinesterase interpretation

Usually no baseline available to compare

Wide range of physiological values

Varying inhibition affinity of various agents

Varying rates of regeneration after inhibition.

Considerable genetic & circadian variation.

Affected by large number of drugs & disease states.

Sample collection must be appropriate

Laboratory reliability.

# Interpreting cholinesterase values.

Parameter	RBC Cholinesterase	Butrylcholinesterase
Advantage	Better reflection of synaptic activity	Easier to assay Declines faster
Site	RBC( reflects CNS gray matter, end plate)	CNS white matter, plasma, liver, heart.
Regeneration(untreated)	1% day	25-30% in first 7-10 days.
Normalization(untreated)	35-49 days	28-42 days
Use	Unsuspected prior exposure with raised plasma cholinesterase	Acute exposure
False depression	Pernicious anemia Hemoglobinopathies Antimalarials Oxalate blood tubes	Cirrhosis Malnutrition Hypersensitivity reactions Succinylcholine, opiates. Pregnancy genetic



# Management of OP poisoning: current strategies.

## **Initial assessment of the unconscious patient**

Check airway, breathing and circulation.

Provide high-flow oxygen & check SaO<sub>2</sub>.

Place the patient in the left lateral position, ideally in a head down position, to reduce the risk of aspiration.

Intubate if necessary.

Watch out for convulsions and treat with intravascular (IV) diazepam immediately if they do occur.

Record a baseline Glasgow Coma Score to help with subsequent monitoring of the patient's condition.

# Decontamination.

Early but only after vitals stabilized.

Forced emesis is contra-indicated.

Gastric lavage only if patient arrives <1-2 hours after ingestion. Use aliquots < 300 ml of saline.

## **Activated charcoal**

A dose of activated charcoal can be left in the stomach at the end of the lavage. There is currently no evidence that either single-dose or multiple-dose regimens of activated charcoal result in clinical benefit after pesticide poisoning.

Patients often have cutaneous & muco-cutaneous exposure.

Contamination of orifices not uncommon.

Thorough body wash can be done as a routine.

# Does the patient require atropine?

## Recognition of OP/carbamate poisoning.

Look for cholinergic features.

Look for five in routine assessment:

1. **Miosis,**
2. **Excessive sweating,**
3. **poor air entry into the lungs due to bronchorrhoea and bronchospasm, bradycardia and**
4. **hypotension.**

Strong history of ingestion but NO features: then observe.

1. ingestion of highly lipophilic agent
2. ingestion of thiol precursor
3. presentation too early.

### **ATROPINE CHALLENGE:**

If the clinical presentation is not clear, administer atropine 0.6–1 mg. A marked increase in heart rate (more than 20–25 beats/min) and flushing of the skin suggest that the patient not have significant cholinergic poisoning and further atropine is not required.

# Loading with atropine and IV fluids

## Dose of atropine

For an unconscious patient, give atropine 1.8–3 mg (three to five 0.6 mg vials) rapidly IV into a fast-flowing IV drip.

Atropine dries secretions and reduces bronchospasm, its administration will improve patient oxygenation.

Onset of action is few minutes( 3-5 minutes).

While waiting for the atropine to have effect, ensure that the two IV drips have been set up (one for fluid and drugs, the other for atropine). Give 500–1000 ml (10–20 ml/kg) of normal saline over 10–20 min.

### Target end-points for atropine therapy

1. Clear chest on auscultation with no wheeze
2. Heart rate >80 beats/min
3. Pupils no longer pinpoint
4. Dry axillae
5. Systolic blood pressure >80 mmHg

**IMPROVEMENT IN ALL 5 PARAMETERS NEEDED.**

Most important parameters are air entry on chest auscultation, heart rate, and blood pressure.

No need to aim for a heart rate of 120–140 beats/min. This suggests atropine toxicity rather than simple reversal of cholinergic poisoning.

Such high heart rates will cause myocardial infarctions in older patients with pre-existing cardiac disease.

### **SIGNS OF UNDER-ATROPINISATION & TACHYCARDIA:**

Hypoxia,  
agitation,  
alcohol withdrawal,  
pneumonia,  
hypovolaemia, and  
fast oxime administration.

If crepitations focal, rule out aspiration.

If miosis is unilateral, likely due to splashes of OPC. Will not reverse with I.V atropine

Common error to focus only on pupil size. Pupil dilatation is sometimes delayed.

## **Patients do not die from constricted pupils!**

It is reasonable to wait for the pupils to dilate. **Check frequently and carefully that the other parameters are improving.**

When all the parameters are satisfactory, the patient has received enough atropine and is 'atropinised'.

If after 3–5 min a consistent improvement across the five parameters has not occurred, then more atropine is required. Double the dose, and continue to double each time that there is no response

**SEVERLY ILL PATIENTS TO BE RAPIDLY ATROPINISED BY CLINICAL JUDGEMENT THAN BY PROTOCOL.**

Once atropinised, start an infusion. In the infusion, give 10–20% of the total amount of atropine that was required to load the patient every hour. AIM FOR A RATE OF 3–5 mg/hour

Monitor.

As atropinisation is lost, give further boluses of atropine until cholinergic signs disappear, and increase the infusion rate

Do not follow heart rate and pupil size because they can be affected depending on the balance of nicotinic and muscarinic features.

### **Markers used to assess atropine toxicity**

1. Confusion
2. Pyrexia
3. Absent bowel sounds (Urinary retention)

The presence of **all three** suggests that too much atropine is being given. Stop the atropine infusion. Check again after 30 min to see whether the features of toxicity have settled.

If not, continue to review every 30 min or so. When they do settle, restart at 70–80% of the previous rate.

## Active cooling and sedation

Hyperthermia is a serious complication

A febrile patient should

receive the minimum amount of atropine needed to control muscarinic signs, sedation if there is excessive agitation and muscle activity, and active cooling.

Reduce agitation with diazepam 10 mg given by slow IV push, repeated as necessary in an adult, up to 30–40 mg per 24 hours.

### **Diazepam is preferred over haloperidol**

1. Large doses of haloperidol may be required in patients receiving atropine.
2. Haloperidol is relatively non-sedating
3. Is associated with disturbances of central thermoregulation
4. Causes prolongation of the QT interval, and
5. Is pro-convulsant.
6. animal studies suggest diazepam reduces damage to the central nervous system & diminishes central respiratory failure



# Oximes in OP Poisoning.

## WHAT IS THE CONTROVERSY?

The clinical benefit of oximes for OP pesticide poisoning is not clear despite decades of use.

Limited by

1. **the type of OP( diethyl or di-methyl)**
2. **poison load,**
3. **time to start of therapy, and**
4. **dose of oxime**

Eddleston M, Szinicz L, Eyer P, Buckley N: Oximes in acute pesticide poisoning: a systematic review of clinical trials. *Q J Med* 2002, 95:275-283.

Current World Health Organization guidelines recommend giving a 30 mg/kg loading dose of pralidoxime over 10–20 min, followed by a continuous infusion of 8–10 mg/kg per hour until clinical recovery (for example 12–24 hours after atropine is no longer required or the patient is extubated) or 7 days, whichever is later.

Eyer P: The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003, 22:165-190

Pralidoxime most commonly used oxime. Available as pralidoxime chloride & mesylate.

Acts mainly on the PNS & CNS entry is limited.

Other available oximes include obidoxime, HI 6 & HLo 7

Main utility is expected to be on the neuro-muscular junction.

Strong in vitro evidence of efficacy.

**Need not however translate into in vivo efficacy.**

1. Insufficient dose
2. Insufficient duration
3. Poor affinity of OP-AchE Complex.
4. Persistence of OP in the patient & re-inhibition of regenerated enzyme.
5. Aging of inhibited enzyme.

Current data suggest that PAM levels of 13.8 mg/dl & obidoxime levels of 3.6 mg/dl necessary. The current WHO regimen will achieve a level of 13 mg/dl in a 70 Kg male.

Basis of current dosage regimen is a 1961 study by Sundwall in cats that 4 mg/l concentration is effective in reversing the effects of a quaternary analogue of sarin.

Extrapolated to all oximes & OPC.

Sundwall. Biochemistry pharmacol 1961;8:413

Increasing recognition of varying affinity of OP-AchE complexes.

Clinically significant OPC's can be classified as diethyl or a di-methyl phosphoryl compound.

Clinical studies have shown that di-ethyl compounds require 20 times PAM cf obidoxime while di-methyl compounds require 7 times PAM

**DI-ETHYL COMPOUNDS BOTH RE-ACTIVATE & AGE SIGNIFICANTLY SLOWER COMPARED TO DI-METHYL COMPOUNDS.**

Aging irreversibly affects enzyme & efficacy limited by this phenomenon.

t<sub>1/2</sub> to aging are 3.7 hours & 33 hours for a dimethyl or diethyl phosphoryl compounds.

Therapeutic windows are thus taken as 4 times t<sub>1/2</sub> or 13 & 132 hours respectively.

## Should one not give oxime therapy in di-methyl poisoning >13 hours??

In vivo data may not hold true to in-vitro data for four reasons.

1. Clinical signs of intoxication become severe at 75–90% inhibition. At such a point, levels of ACh are increased and tend to compete with the OP oxon. This will reduce the rate of further inhibition of AchE. Thus, the state of complete inhibition is more difficult to reach *in vivo than in vitro*.
2. Signs appear first while about 50% of AChE remains uninhibited and some molecules of AChE will only become inhibited and open to ageing long after this.
3. Even when signs of intoxication are marked, some spontaneous reactivation will be proceeding; re-inhibition by persistent inhibitor may be less rapid than in the *in vitro test situation*.
4. As soon as an effective concentration of oxime is achieved *in vivo the balance of ageing and reactivation reaction rates for the inhibited AChE is altered in favour of the latter*.

Therapy is probably justified > 13 hours.

# Clinical data on oximes in OPC.

Have been conflicting. Most studies failed to show a benefit of oximes

Most have, however, not used the standard WHO approved regimen.

Have thus been interpreted as a failure to achieve appropriate levels at the right time.

3,122 articles on organophosphate poisoning published.

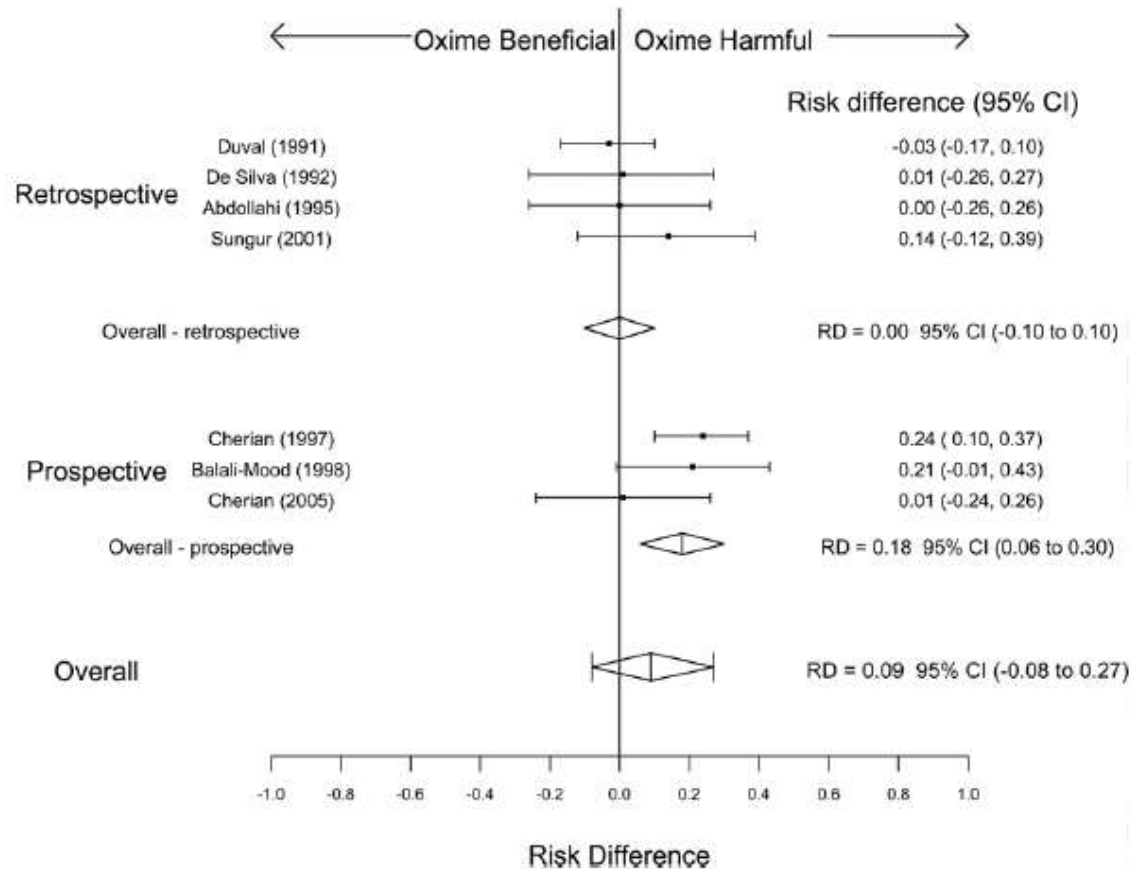
116 related to oxime use in human organophosphate poisoning.

Seven trials, including two randomized controlled trials, compared oximes with standard medical care(placebo controlled trials).

Several smaller uncontrolled trials reported.

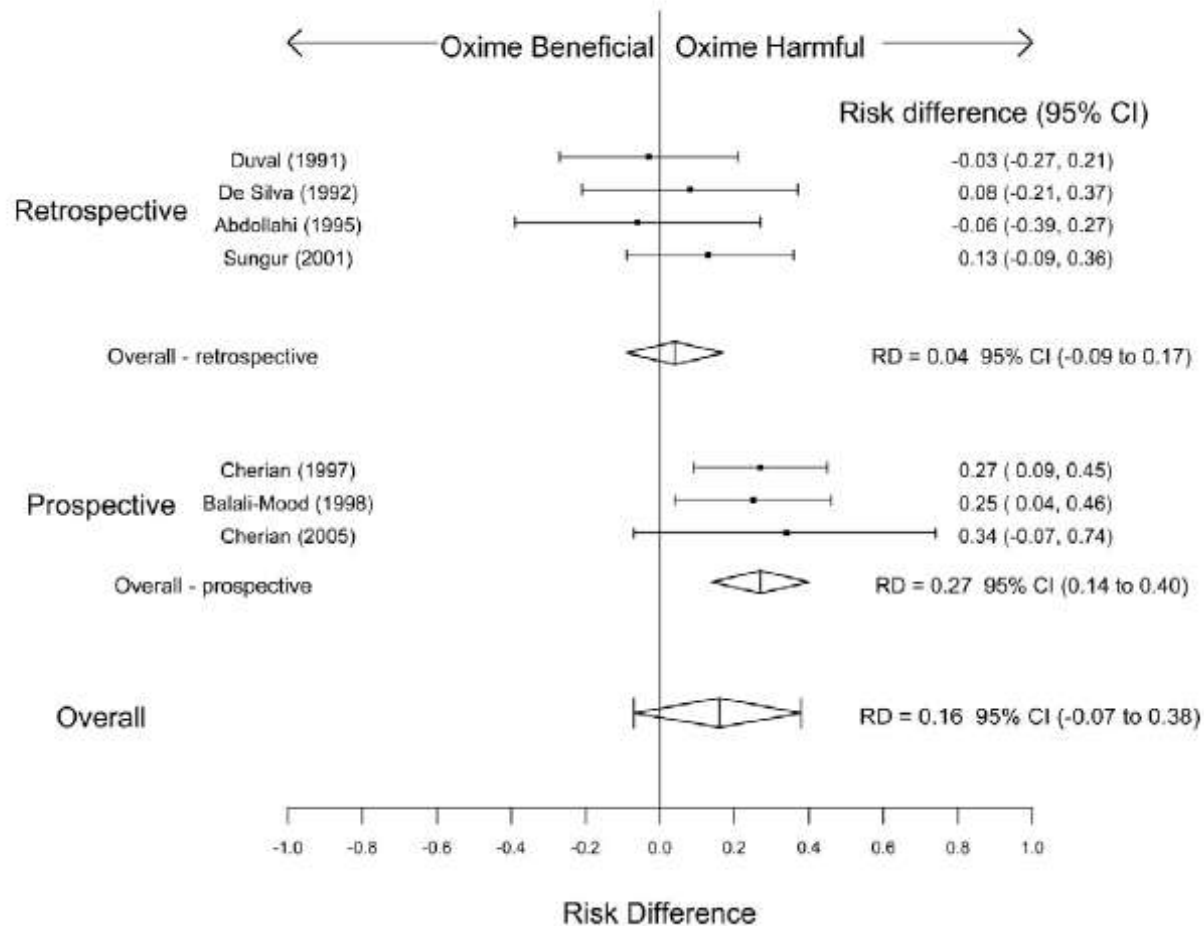
2 systematic reviews(in 2002 & 2005 evaluating 182 patients in 2 RCT'S) and one meta-analysis reported.

# 1. Association between oxime therapy and mortality



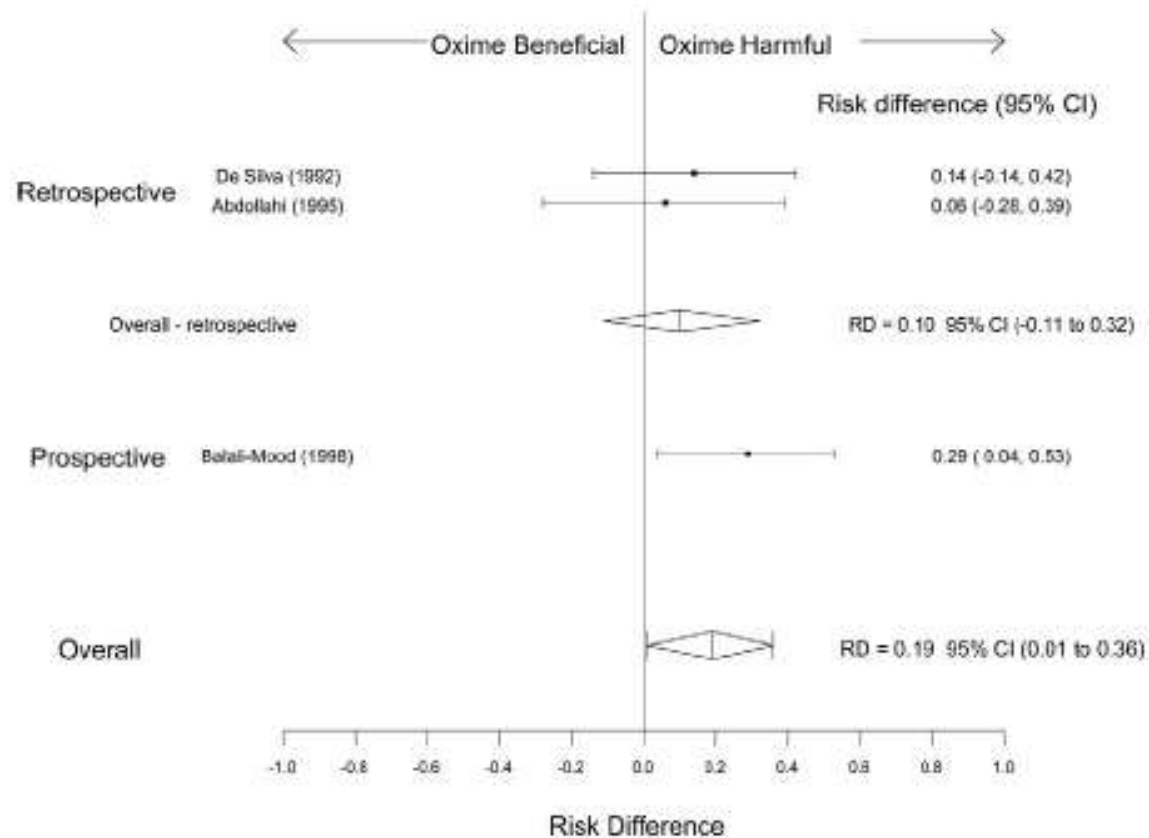
**Oxime therapy and outcomes in human organophosphate poisoning: An evaluation using meta-analytic techniques Crit Care Med 2006; 34:502–510**

# Association between oxime therapy and the need for ventilatory support



**Oxime therapy and outcomes in human organophosphate poisoning: An evaluation using meta-analytic techniques Crit Care Med 2006; 34:502–510**

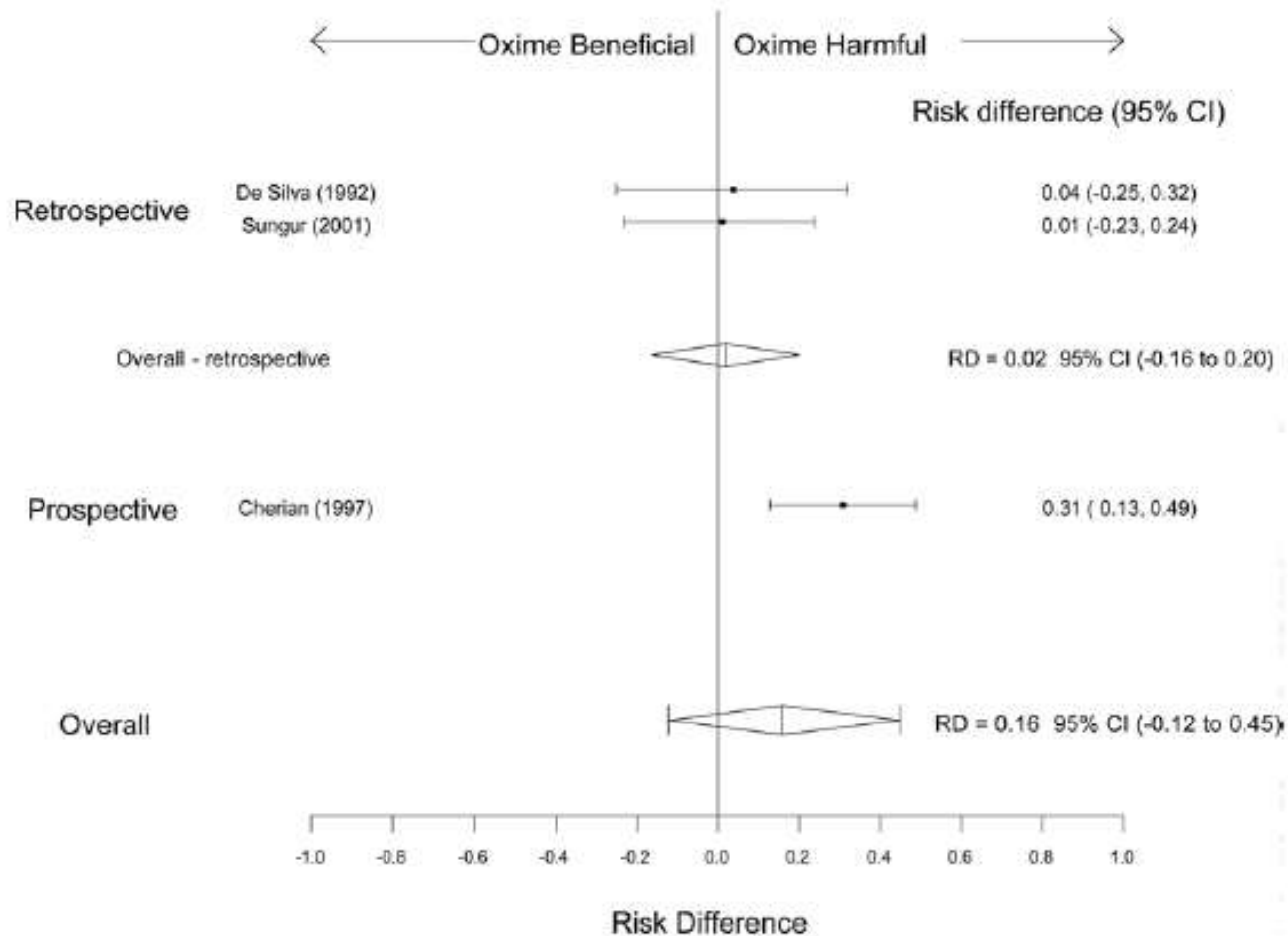
# Forest plot representation of the association between oxime therapy and need for intensive care therapy



**Oxime therapy and outcomes in human organophosphate poisoning: An evaluation using meta-analytic techniques Crit Care Med 2006; 34:502–510**



## Association between the effect of oxime therapy and the incidence of intermediate syndrome



**Oxime therapy and outcomes in human organophosphate poisoning: An evaluation using meta-analytic techniques Crit Care Med 2006; 34:502–510**

## The two published RCTs of pralidoxime

RCT 1 (Aug 91?Dec 92)

RCT 2 (Dates uncertain)

Controls (?Low-dose?)    Cases (?High-dose?)

Controls

Cases

n	36	36	55	55
Dose (estimated/ loading dose)	Bolus: 22/mg/kg  No infusion	No bolus  Day 1: 5.6 mg/kg/h	Placebo saline only  Days 1?3: 3.7 mg/kg/h Day 2: 2.8 mg/kg/h Day 3: 1.8 mg/kg/h Day 4: 0.9 mg/kg/h	No bolus
Pesticides				
Dimethyl OPs	56%	61%	Not stated	Not stated
Diethyl OPs	25%	22%		
Unknown	19%	17%		
Time from ingestion to Rx	<6 h    8	3	<5 h    14	8
	6-12 h    6	14	6-10 h    13	15
	12-24 h    15	10	11-15 h    12	9
	24-36 h    5	5	16-20 h    4	9
	36-48 h    2	4	>21 h    10	9
Cholinesterase levels	338.9 (260.5)	441.3 (450.3)	743.7 (1254)	283.2 (243)
Outcomes				
Deaths	5 (14%)	8 (22%)	3 (5%)	16 (29%)
Ventilated	17 (47%)	24 (67%)	22 (40%)	37 (67%)
Intermediate syndrome	13 (36%)	20 (56%)	19 (35%)	36 (65%)

This first RCT reported

1. an increased mortality rate (22% vs. 14%; OR 1.77, 95%CI 0.52–6.0) and
2. increased requirement for ventilation (67% vs. 47%; OR 2.04, 95%CI 0.78–5.3)

among patients who received the infusion, compared to those who received the bolus dose.

Johnson S Evaluation of two treatment regimens of pralidoxime in the management of organophosphorus poisoning. A randomized, double blind controlled clinical trial. *J Assoc Physicians India* 1996; 44:529–531

Following on from RCT 1 it compared ‘high-dose’ pralidoxime (i.e. 12 g by continuous infusion without loading dose) with placebo saline infusion in 110 patients. The ‘high-dose’ regimen was associated with

1. a significantly higher risk of death (29% vs. 5%; OR 7.1, 95%CI 1.9–26.0) and
2. requirement for ventilation (67% vs. 40%; OR 3.1, 95%CI 1.4–6.7).

Cherian AM Effectiveness of P2AM (PAM–Pralidoxime) in the treatment of organophosphate poisoning (OPP). A randomized, double blind placebo controlled clinical trial. *J Assoc Physicians India* 1997; 45:22–24

DATA IN THE POST-OXIME ERA IN CMC VELLORE SHOWS MORTALITY SIMILAR TO CURRENT FIGURES WORLDWIDE WITH OXIMES( mortality -14%)

# Criticisms of the 2 RCT'S in OPC.

Studies did not include data on nature of compound.

Methodology unclear. Have not used the current CONSORT guidelines

Did not use the WHO approved regime in OPC.

'high-dose' regimen of pralidoxime used in Vellore may not produce an effective plasma concentration.

Pharmacokinetic studies have shown that 1 g given over 30 min to patients with a mean weight of 72 kg (SD 8.5) falls below a plasma concentration of 4 mg/l within 1.5 h.

Furthermore, recent studies have suggested that even 4 mg/l may actually be insufficient for many pesticides.

loading dose of pralidoxime is required to reach an effective plasma concentration and that a bolus dose alone, while producing an effective concentration for only several hours, offers some benefit

However, the worse outcome seen in patients who received pralidoxime in RCT 2 suggests that the pralidoxime infusion harms patients.

An alternative explanation is that features of the RCT itself led to this result. Neither power calculations nor stopping rules are presented in the published papers

Sicker patients might also have been randomized to the intervention arm of RCT 2, which had much reduced mean pseudocholinesterase levels at baseline

No information on masking is given, and a block size of four was used in both studies. Masking might thus have been inadequate.

**Later studies, though non-randomized have found a role for oxime therapy in organophosphorus poisoning.**

Singh S, Chaudhry D, Behera D, Gupta D, Jindal SK. Aggressive atropinisation and continuous pralidoxime (2-PAM) infusion in patients with severe organophosphate poisoning: experience of a northwest Indian hospital. *Human Exp Toxicol*2001; 20:15–18.

Zheng G, Song S, Li M. Comparison of effects between concentrated-dose and non-concentrated-dose pralidoxime chloride on respiratory muscle paralysis in acute organophosphorus pesticide poisoning. *Zhonghua Nei Ke Za Zhi*2000; 39:655–7

Shivakumar.( Stanley medical college investigators) *J Assoc Phys India* 2006; 54: 250

## Conclusion on role of oxime therapy in OPC poisoning.

A large high-quality RCT comparing the current WHO-recommended regimen with placebo is required to definitively assess the value of pralidoxime in acute OP poisoning.

Randomization should be stratified according

1. to baseline severity,
2. time to presentation, and
3. class of OP pesticide taken (diethyl or dimethyl), with predefined sub-group hypotheses.

Because of the importance of ageing in determining the usefulness of oximes, red blood cell AChE activity and the potential for ex-vivo reactivation will have to be measured for such a study to be fully interpretable.

**Till such a time that data is available, it is justified to use the WHO approved regime & oximes in Organophosphorus poisoning.**

# Other therapies.

**Diazepam** can be an excellent adjunct antidote in severe cases. It appears more effective than other anticonvulsants. Prophylactically in ALL severe intoxications.

Anti-GABA-ergic properties of diazepam enable it to act as a specific antagonist in secondary GABA-ergic central pathways activated by ACh.

Counteracts some of the undesired CNS side effects of atropine.

The role of hydrocortisone and antibiotic treatment after aspiration is not known.

Alcohol co-ingestion requires assessment of blood sugar levels and vitamin B supplementation.

Monitor regularly for

1. Development of neuromuscular weakness s/o intermediate syndrome.
2. Recurrence of toxicity in potent, lipophilic agents.
3. Complications of ventilation, atropine & oximes.

# WHAT IS THERE FOR THE FUTURE?

Accumulation of acetylcholine in the central nervous system is believed to account for the rapid lethality of organophosphate pesticides and chemical nerve agents

Study in rats pre-treated with anti-cholinergics & challenged with OP agent.

Pretreatment with diazepam (3/9 deaths), or xylazine (3/9), decreased lethality substantially. Intermediate doses of morphine (3.1 to 5.5 mg/kg) resulted in survival, but higher doses did not. Ketamine (7/8 deaths) was ineffective as an antidote. Survival times also were prolonged in the diazepam and xylazine groups

Sivilotti M A Multiple Centrally Acting Antidotes Protect against Severe Organophosphate Toxicity Acad Emerg Med 2006; 13:359–364

Another drug that has shown some beneficial effect in organophosphorus poisoning is Magnesium. The actual role of magnesium in the management of organophosphorus poisoning remains to be studied in randomized controlled trials.

Singh G, Neurophysiological monitoring of pharmacological manipulation in acute organophosphate poisoning. The effect of pralidoxime, magnesium sulfate and pancuronium. Electroencephalog Clin Neurophysiol 1998; 107 : 140-148.