ABSTRACT
Organophosphorus (OP) compounds which are in use since 1940s worldwide as insecticides have been a source of poisoning and continue to pose management problems. Resuscitation, Decontamination, Specific antidote, and supportive measures continue to be the mainstay of therapy. Different authors have prescribed different therapeutic regimens leading to controversies. This paper aims at offering a comprehensive guideline on these aspects of management. Decontamination of the body by washing with soap and water is to be thorough and complete. A repeat stomach wash in every case is recommended to remove residual OP. Atropine is the only life saving antidote and is to be started along with decontamination. Out of 38 protocols prescribed in literature a protocol of starting with dose of 1-2 mg followed by bolus doses, every 5 min, with double of previous dose, in case of no response, to achieve the target end point is recommended. Thereafter it is to be maintained through Atropine infusion (at a rate of 10-20% of total atropine required to load the patient per hour) for 24-48 hrs and gradually withdrawn over next 3-5 days. Clearance of chest of secretions and maintenance of BP has been given more importance in the target point than size of pupil and heart rate. Glycopyrrolate is recommended as an adjunct to atropine to control secretions or when atropine toxicity is confused with OP toxicity. The role of Oximes has been questioned by different workers both from India and abroad. Though it has been shown to re-activate RBC cholinesterase the causes of failure to benefit have not been properly established. Because the idea is sound it is appropriate to recommend Pralidoxime to start as early as possible with a loading dose of 30 mg/kg IV to be given over 30 minutes to be followed by a continuous infusion of 8-10 mg/kg/hr until clinical recovery or seven days whichever is later. Ventilation is the most useful life saving advance in supportive care. Criterias for ventilation have been defined. Use of tranquilizer has been recommended to be liberal. Poisoning effect of solvent in OP compounds contributing to chemical pneumonitis is to be kept in mind. The need of close observation through OP obs sheet has been stressed. Use of fluids, diuretics, antibiotics etc has been discussed.

Introduction: - Organophosphorus (OP) compounds first synthesized in early 1800s were developed as insecticides in early 1900s and found world wide application by 1941. (I)

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Intoxication by these agents continues to be a therapeutic problem. Possibility of exposure during war/terrorist activities is increasing. Resuscitation, decontamination, early use of specific antidote, close observation and good supportive care form the basis of management. Despite large number of cases being reported world wide, the current evidence base is small. (2) Text books recommend varied therapeutic antidote regimens leading to controversies and confusion. In this paper it is intended to offer a comprehensive guideline so that junior physicians can manage such acute poisoning cases efficiently. Before proceeding to management guidelines it will be proper to review the pharmacodynamics of the OP compounds, so that the rationale behind the guidelines will be well appreciated.

Pharmacodynamics: - Organophosphates/carbamates inactivate the enzyme Cholinesterase (ChE) by reacting at the esterase site, which leads to an increase in Acetylcholine (ACh) at the muscarinic receptors, nicotinic receptors and in CNS leading to toxic effects. The phosphorylated/carbamated enzyme complex subsequently undergoes hydrolysis spontaneously (carbamated complexes within minutes to hours whereas phosphorylated enzyme complexes take some 60 minutes to several weeks). The reactivation time can be enhanced by oximes. Once OP enzyme complex looses the alkyl group (Ageing) it can not be reactivated. (3) OP compounds can be absorbed through skin, conjunctiva, oral mucosa, GI tract, respiratory tract, by direct contact, ingestion, inhalation and injection. The hydrocarbon solvent also produces its effects. Most patients become symptomatic rapidly, though the onset and severity of symptoms depend on the nature of the compound, amount, route of exposure and rate of metabolic degradation. After absorption they are rapidly distributed in all body tissues. Lipid solubility makes easy access to CNS and fat stores. They are intermittently released from fat stores to circulation/secreted to stomach and have been incriminated for the sudden deterioration in a stable patient. Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half life of minutes to hours. Elimination occurs via urine bile and faeces. Toxic effects of excreted products
Organophosphorus Poisoning: Current management guidelines

Clinical features: They are due to stimulation of muscarinic, nicotinic and central receptors. Onset is usually within 30 min to 03 hrs. This may be delayed depending on the type of OP, route of exposure and amount of systemic poison. The severity of poisoning has been graded as mild, moderate and severe. (Table-1)(4) The end result may be a multi system event. Most fatality occurs within 24 hrs.


Management: OP poisoning is a medical emergency. They need to be nursed in general ICU with adequate ventilation unless specific complications need Specific ICU care. The health care workers need protection through personnel protective equipments. Rubber Gloves and gowns are recommended as these compounds are known to penetrate latex/ vinyl gloves. Charcoal cartridge masks are recommended for respiratory protection. The staff may need to be rotated if they can't stand the noxious order.

Decontamination: Besides, the decontamination at the site, in the emergency department all clothing, hair accessories are to be removed and placed in appropriate waste bags. The person is to be washed with copious amount of water and soap (OPs are hydrolyzed in an aqueous solution in high PH). Skin folds and underside of fingernails and long hairs require particular attention. Ocular decontamination is to be carried out by washing eyes with water/normal saline. Incontinent patient requires repeat wash. Attention should not be diverted from ABC of Cardiopulmonary resuscitation. Seizures are to be controlled by appropriate measures. Two IV lines be secured and blood samples for haematological and biochemical and ChE be collected. ECG be recorded. Laboured breathing, sweating, pin point pupil would suggest OP/carbamate poisoning. Fig-1 Antidote inj atropine should be started immediately which should not be withheld even if oxygen is not available. There is no good evidence that giving atropine to a cyanosed patient would cause harm. (5)

In case clinical presentation is not clear Inj. Atropine 0.6 mg to 1.0 mg may be given IV. Increase in heart rate by more than 20-25 beats/min and flushing would suggest that the patient does not have significant cholinergic poisoning and further observation required. While observing effects of atropine give 500-1000 ml of Normal saline (10-20 ml/kg) over 10-20 min to compensate fluid loss due to sweating, diarrhoea and cholinergic hyper-secretion. There is no evidence that it will harm the patient with bronchorrhoea as long as atropine is being given. (5) History of alcohol ingestion should be enquired as well as possibility of other poison being consumed be ascertained.

Active cooling and sedation: Cooling is indicated if the patient is febrile and climate is hot & humid. Agitated patient need to be sedated with Inj. Diazepam 10 mg IV slowly which can be repeated up to 30-40 mg/24 hrs. Diazepam will help in allaying anxiety, facilitate gastric lavage, reduce damage to CNS (6), diminish central respiratory failure (7) and control seizure.

Gastric Decontamination: Forced emesis and syrup Ipecac have no role. (8) Gastric lavage is indicated once patient is stabilized, calm enough to give consent and in unconscious intubated patient, which is recommended to be repeated after 2-3 hrs (9). Though it has been recommended only to be carried out within 1-2 hours of ingestion of OP/carbamate elsewhere it has been started even after 12 hrs of ingestion and repeated thrice at an interval of 4 hrs (10). Repeat stomach wash will remove the residual poison if any/secreted to stomach subsequently from fat stores. After aspirating the contents of stomach through stomach tube (if food particles are present)/Ryle’s tube, water or normal saline in lots of 300 ml be given and be aspirated. Continue it till the returning

Table 1: Grading Severity of Organophosphate Poisoning

<table>
<thead>
<tr>
<th>Grade</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
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<tbody>
<tr>
<td>Walks and talks</td>
<td>Cannot walk</td>
<td>Unconscious, no papillary reflex, Muscle paralysis</td>
<td></td>
</tr>
<tr>
<td>Headache, dizzy</td>
<td>Soft voice</td>
<td>Increased bronchial secretions, Dyspnoea</td>
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<td>Nausea, Vomiting</td>
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<td>Abdominal pain</td>
<td>(fasciculations)</td>
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<td></td>
</tr>
<tr>
<td>Sweating, salivation</td>
<td>Anxiety, restlessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Small pupils (miosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum acetylcholinesterase level (%)</td>
<td>1.6-4.0 u/l</td>
<td>Results: 0.8-2.0 u/l</td>
<td>Results: &lt; 0.8 u/l</td>
</tr>
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</table>

Fig. 1: Showing pin point pupil in a case of OP poisoning

rubber locally in form of burns over gluteal region, natal cleft and thighs have been noted.

Rubber Gloves and gowns are recommended as these compounds are known to penetrate latex/ vinyl gloves. Charcoal cartridge masks are recommended for respiratory protection. The staff may need to be rotated if they can’t stand the noxious order.

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injection. hence, one need not wait for more than five minutes
The peak effect of atropine is seen within three minutes of an IV
escalated (doubled each time) to achieve atropinisation quite
be low (1-2 mg) so as to cater for milder cases and then rapidly
heart rate > 80 beats/min
Pupil no longer pin point
Dry axilla
Systolic blood pressure > 80 mm of Hg
fluid is colourless and odourless. Ensure that no fluid is left inside
the stomach by measuring the fluid taken off.
Activated Charcoal: - Though there is no evidence that either
single dose or multiple dose regimens of active charcoal will
result in benefit yet a dose of charcoal (50 gm) can be left in the
stomach (11, 12).
Transfer to ICU: - Atropine and resuscitation measures are to be
continued and vitals recorded while transferring to ICU. Patients
with the following criteria may need ventilator support.(13)
History of intake of large dose
Copious secretions
Disturbed level of consciousness
Signs of hypoventilation or respiratory obstruction by secretions
Hence intubation and ventilation facilities should be ensured to
be available in ICU. Patient is to be placed on monitor. Parameters
including oxygen saturation are to be observed and recorded in
OP/Carbamate observation sheet. Table – 2(5).
Antidote: - Anticholinergics are competitive antagonist to Ach
and reverse all muscarinic activities both in CNS and peripheral
nervous system. Inj.Atropine is the only life saving antidote. Full
and early atropinisation is an essential and simple part of early
management. Clinical toxicology text books describe varied
atropine regimes. The sum total of 38 regimes found in literature
is to start a Bolus loading dose followed by boluses after a fixed
time interval varying from 5-15-30 min till atropinisation or Bolus
loading dose followed by infusion (14).The latter regimen showed
improved outcome. (15) Although the benefit of infusion is not
yet proven this regime saves time, requires less observation,
produces less fluctuation in plasma atropine concentration and
makes weaning easier.(16) The dose of atropine recommended to
be low (1-2 mg) so as to cater for milder cases and then rapidly
escalated (doubled each time) to achieve atropinisation quite
fast. Alternatively it started with a bigger dose (5 mg) to ensure
rapid atropinisation. Because of danger of over atropinisation the
former practice offers more control by starting with low doses.
The peak effect of atropine is seen within three minutes of an IV
injection. Hence, one need not wait for more than five minutes
before giving another bolus. Though the authors acknowledged

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart rate</th>
<th>Clear lung</th>
<th>Pupil</th>
<th>Dry axilla</th>
<th>BP</th>
<th>Bowel sounds</th>
<th>Mental state</th>
<th>Fever &gt;37.5c</th>
<th>SPO2</th>
<th>Remarks</th>
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</thead>
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**Table 3: Target end points for atropine therapy**

Clear chest on auscultation with no wheeze
Heart rate > 80 beats/min
Pupil no longer pin point
Dry axilla
Systolic blood pressure > 80 mm of Hg

Atropine toxicity: - Confusion, agitation, hyperthermia, ileus,
tachycardia etc would suggest over atropinisation which would
necessitate discontinuation of the atropine infusion, followed by
frequent observation. When they settle down the infusion is to
be started at 70- 80 % of the previous rate. Hyperthermia is a
serious complication in hot wards which needs prevention. To
avoid preservative toxicity powder atropine be reconstituted in
normal saline and be used.

**Duration of maintenance atropine therapy:** - This depends on
the severity and response to therapy. Usually it is maintained for
24- 48 hrs or longer in severe cases, and gradually withdrawn
over 3-5 days. Frequent observation is required to detect early
signs of intermediate syndrome. Tidal volume and blood gases
are to be measured. Indications for ventilation have been spelt
out. Table- 4 (3).

**Glycopyrrolate:** - Some studies have shown that glycopyrrolate
**Table 4: Guidelines for ventilator support**

<table>
<thead>
<tr>
<th>I. Respiratory Gas Tensions</th>
</tr>
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<tr>
<td>i. Direct Indices</td>
</tr>
<tr>
<td>Arterial Oxygen Tension &lt; 50 mm Hg on room air</td>
</tr>
<tr>
<td>Arterial CO₂ Tension &gt; 50 mm Hg in the absence of metabolic alkalosis</td>
</tr>
<tr>
<td>ii. Derived Indices</td>
</tr>
<tr>
<td>PA-aO₂/Fio₂ &lt; 250 mm of Hg</td>
</tr>
<tr>
<td>PA-aO₂, (Pulmonary arterial-alveolar O₂ gradient) &gt; 350 mm of Hg</td>
</tr>
<tr>
<td>Vd/Vt &gt; 0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Clinical - Respiratory Rate (RR) &gt; 35 breaths/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>III. Mechanical Indices</td>
</tr>
<tr>
<td>Tidal Volume 5 ml/kg</td>
</tr>
<tr>
<td>Vital capacity &lt; 15 ml/kg</td>
</tr>
<tr>
<td>Maximum inspiratory force &lt; 25 cm of H₂O</td>
</tr>
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**Table 5: Equivalent dosing units of pralidoxine salts**

<table>
<thead>
<tr>
<th>Salt</th>
<th>Equivalent dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralidoxine chloride</td>
<td>1.00</td>
</tr>
<tr>
<td>Pralidoxine mesilate</td>
<td>1.34</td>
</tr>
<tr>
<td>Pralidoxine metilsulfate</td>
<td>1.43</td>
</tr>
<tr>
<td>Pralidoxine iodide</td>
<td>1.53</td>
</tr>
</tbody>
</table>

is equally effective with fewer central nervous system side effects and better control of secretions. Since it does not enter CNS initial muscarinic signs like coma or drowsiness will not respond. Hence it’s use is recommended when there is copious secretion as an adjunct to atropine or when features of atropine toxicity like delirium etc are confused with CNS effects of poison or when atropine is not available. Ampoules of 7.5 mg of glycopyrolate in 200ml of saline is started as infusion and is titrated to the desired effects of dry mucus membranes. (18) It has also been given at a dose of 0.2mg IM stat and repeated 6hrly if required. Diphenhydramine can be an alternate centrally acting anticholinergic agent if atropine is not available (19).

Magnesium Therapy: Magnesium therapy in addition to atropine and oximes has been found to benefit. The mechanism appears to be inhibition of AChE and OP antagonism. (20)

Cholinesterase Reactivators: These agents known as oximes get attached to the free anionic site of the enzyme ChE. The oxime end then reacts with the phosphorus atom of OP attached at the esteratic site of the enzyme. This oxime phosphate so formed diffuses away from the enzyme and has a direct action in converting the OP to a harmless compound (21). Reactivation of ChE is more marked in the skeletal muscle than at autonomic site and not at all in CNS (Do not enter CNS). Thus their use in OP poisoning is secondary to that of atropine. Oximes (Pralidoxime, Obidoxime) are widely used since 1955 in OP poisoning along with atropine within 24-48 hours post ingestion as pralidoxime chloride 1 gm every 3-4h for 1-3 days WHO guidelines recommended giving a 30 mg/kg loading dose of Pralidoxime over 10-20 min followed by a continuous infusion of 8-10 mg/kg/hr until clinical recovery or seven days have elapsed whichever is later. Where obidoxime is available a loading dose of 250 mg is followed by an infusion of 750 mg every 24 hrs. Their efficacy however has been questioned over last two decades by workers from Sri Lanka, South Africa, Taiwan, Iran and India. All these studies have been criticized either on the basis of non comparable groups of selected patients or inadequate doses of PAM (9). Though these studies have demonstrated clear reactivation of red cell acetylcholinesterase in diethyl OP pesticide poisoned patient (ageing in this compound AChE complex takes much longer than Dimethyl OPs) the reason for their failure to benefit was not apparent. (22) Further studies on different regimens or different oximes have been recommended by these workers while proposing type of OP and its coformulant, poison load, time to start of therapy and the dose of oxime being the limiting factors. (23)

Since the idea is sound and animal experiments suggest it is useful, it is recommended preferably in moderate to severe cases. (9, 24) It is to be administered as early as possible post ingestion to offer benefit. Delayed presentation is not a contraindication (4). There are no definite dose recommendations. However, it has been established that the therapeutically effective oxime concentration in plasma is 4mg/litre though effect has been demonstrated in lower concentration as well. Elsewhere it has been used as 2gm loading followed by 1gm/h for 48h by infusion (high dose) with benefit, concluding (25) that administration in high dose and constant infusion is better than repeated bolus administration. A low dose schedule (1gm bolus) has also shown lower mortality suggesting that the bolus dose do achieve a therapeutic concentration for a limited amount of time (26).

In view of above though guide lines are not definite, it is clear that oximes are effective when given early and in high doses (dose to be adjusted depending on the salt used) that too a bolus dose offers benefit which is to be followed by infusion for a sufficient duration (therapeutic window for Diethyl AChE complex is 133h) Table-5 (27). Keeping these aspects in mind the guidelines followed by Southern Hospitals Network appears most appropriate and is recommended as Initial bolus dose of 2gm IV (30mg/kg) over 30 min (rapid administration leads to complications ) which is to be followed by 1 gm IV every 8 hours in mild to moderate poisoning and in severe poisoning cases 500 mg/hour (8-10mg/kg/h) till clinical recovery (12-24h after atropine no longer required or the patient is extubated) or 7 days which is later. Repeat bolus/infusion is to be ceased based on clinical testing or plasma ChE test. (4) Though oximes are not recommended for Carbamate poisoning, their use should not be withheld in case of unknown cholinergic poisoning as definite harm to human beings has not been demonstrated. (5)

**Ventilation:** This is the most useful advance in the management of OP poisoning and makes all the difference on outcome. Indications for ventilation have already been talked above. Regular and close observation in initial course will guide when to ventilate. Succinylcholine is to be avoided. Non-depolarising neuromuscular blocking agents require higher doses to show effect.
Furosemide: - It is recommended if pulmonary oedema persists, even after full atropinisation.

Hydrocarbon Aspiration: - In case of ingestion of liquid concentrates of OP, hydrocarbon solvent aspiration causes chemical pneumonitis. These cases are to be managed as a case of Acute Respiratory Distress Syndrome.

Antibiotics: - Broad spectrum antibiotics are to be instituted as per antibiotics policy of the institution, considering the risk of infection due to frequent and multiple interventions.

Agitation/Convulsion: - Causes of agitation unrelated to pesticide toxicity like alcohol withdrawal/full bladder unless catheterized/head injury etc are to be excluded. Role of Diazepam has already been described and is preferred over haloperidol. Intraosseous (Bone injection Gun, BIG) Midzolam demonstrated rapid peak concentration in swine compared to IV or IM route, can be used to control convulsion.(5)

Injected OP poisoning: - The effects OP poisoning are severe and requires higher doses of antidotes. Local tissue necrosis may need surgical intervention. All oily based OP need to be removed to avoid systemic absorption (28).

Summary of treatment protocol is given in figure-2.(10)

Contraindications: - Drugs like morphine, succinylcholine, theophylline, phenothiazine and reserpine are contraindicated. Adrenergic amines should be given only if there is specific indication, such as marked by hypotension.

Conclusion: - Medical management of Organophosphorus pesticide poisoning demands close observation, timely institution of antidote in adequate doses and duration and good supportive care. Though available evidence is lacking in many aspects of different controversies, attempt has been made to define them and offer a pragmatic therapeutic protocol which will enable junior physicians to manage these patients with confidence and success.

REFERENCES


3. Davies DR, Green AL. The kinetics of reactivation by oximes of cho-


