Organophosphate Compound Poisoning

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ABSTRACT

Acute organophosphorus (OP) pesticide poisoning is a major clinical problem in the developing world[1, 2, 3] The World Health Organization (WHO) estimates the number of acute pesticide poisoning at 3 million cases per year and mortality of 3, 00,000deaths per year[4]. Most of these pesticide poisoning and subsequent death occur in developing countries following a deliberate self ingestion of the poison. Metacid (Methyl Parathion) and Nuvan (Dichlorovos) is popular Organophosphorus compound used for deliberate self harm in Nepal

The Organophosphorus inhibites cholinesterase activity leads to accumulation of acetylcholine at synapses, causing overstimulation and disruption of neurotransmission in both central and peripheral nervous systems. Exaggerated manifestations of nicotinic and muscarinic receptors appear as a result of these actions.

Diagnosis of poisoning is done with history of exposure to pesticides, characteristic signs of toxicity and improvement of condition with Atropine. Supportive management of poisoning follows rapid initial management of airways, breathing and circulation

Gastic lavage and administration of charcoal is done routinely with decontaminating procedure. Cholinesterase reactivates e is an important part of management, but benefit is not well confirmed in clinical trails

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INTRODUCTION

Pesticide self-poisoning is a major clinical problem in many parts of the world [5,6] probably killing about 300,000 people every year.[7, 8] Although most deaths occur in rural areas of the developing world.[6] Pesticide poisoning is also a problem in industrialized countries, where it may account for a significant proportion of the deaths from self-poisoning that do occur. [9,10]

Acute Organophosphorous compound (OPC) poisoning is a known cause of acute poisoning, in Nepal, with high mortality. And it is also a common cause of medical admissions and deaths in Nepalese hospitals.[11-16] Thirty-one percent of all suicidal deaths in the country in 1999-2000 were due to poisoning.[12] Hospital- based studies from five major hospitals across the country in 1999-2000 showed OP compounds were the most common form of poisoning comprising 52% of total cases.[13] Various isolated hospital-based studies also clearly demonstrate that OP compounds occupy the greatest burden of poisoning related morbidity and mortality in Nepal. [16-21]

Hospital based data from across our country Nepal shows that Methyl –Parathion, Diclovorovos, and Dimethoate etc are the common OPs related human poisoning. Metacid a popular brand for Methyl parathion is the most frequent ingested and probably the most toxic organophosphate used for poisoning in Nepal. Dichlorovos, which is known as Nuvan is moderately volatile solution. Dimethoate has a lethal dose of 10-12 gm and there are concerns that it causes specific cardiac toxicities in addition to cholinergic syndromes. Malathon is relatively less toxic and is used for the treatment of Pediculosis.Lethal dose is 1 gm/kg in mammal

Clinical features of poisoning

The acute features of poisoning generally develop within 1–2 hours of exposure and can be grouped as those related to the muscarinic, nicotinic and central nervous system. Muscarinic or parasympathetic features include salivation, lacrimation, urination, defecation, gastrointestinal cramps and emesis, and can be remembered by the acronym SLUDGE. Another acronym, DUMBLES (diarrhoea, urination, miosis, bronchorrhoea, lacrimation, emesis and seizures/sweating/salivation) also includes all the clinical features.Bronchorrhoea and bronchospasm may be severe. Miosis, hypotension and bradycardia are key features and need to be assessed. Nicotinic or somatic motor and sympathetic features include fasciculations, muscle cramps, fatigue, paralysis, tachycardia, hypertension and rarely mydriasis. Neurological features include headache, tremors, restlessness, ataxia, weakness, emotional liability, confusion, slurring, coma and seizures.

The Three Phases of OP Poisoning

After an exposure to an OP agent the clinical syndrome progresses through three well defined phases: Initial Cholinergic Phase, Intermediate Syndrome and Delayed Polyneuropathy phase

Initial Cholinergic Phase

The first stage is known as the Initial Cholinergic Phase. This first phase is a medical emergency that requires rapid treatment. This phase is marked by an increase in nasal, oral, lacrimal, and bronchial secretions, bronchoconstriction, sweating, vomiting and GI distress with increased motility and cramping.[18] Miosis is also common and generally results in blurred vision. An interesting note is that a majority of patients from the sarin attack in the Tokyo subway had a chief complaint of eye pain.[18]During this phase you can also see muscle fasciculations, which can progress to flaccid paralysis if acetylcholine accumulates in the nicotinic sites at the neuromuscular junctions. The CNS signs and symptoms are drowsiness, HA, insomnia, and or confusion as the acetylcholinesterase is inhibited in the brain. Severe exposures lead to seizures, slurred speech, and or coma with decreased respiratory drive.[3] Death is common during this phase mostly due to the cardiac effects that occur. Bradycardia and other arrhythmias can occur in combination with respiratory depression and CNS depression. This phase generally lasts from 24- 48 hours.

Intermediate Syndrome

The second phase is the intermediate syndrome and is characterized by the onset of muscle weakness. The muscle weakness affects respiratory muscles, such as the diaphragm. Typically an onset of SOB occurs with progressive use of accessory muscles and can rapidly result in death due to respiratory insufficiency. This phase begins after about 1-4 days and complete recovery can occur within 4-18 days with appropriate ventilatory support.[18]

Also note that during this phase, in the presence of anticholinesterase agents, excessive calcium (Ca++) is mobilized and can cause desensitization of postsynaptic

nicotinic receptors. This leads to the release of both contractile and noncontractile forms of Ca++ at the neuromuscular junction following any nerve stimulation.

Noncontractile Ca++ mobilization was shown in desensitizing conditions depending on the amount of acetylcholine that had accumulated in the synaptic cleft of neuromuscular junctions. The mechanism that leads to this release is presumed to be brought on by prolonged postsynaptic receptor activation by acetylcholine. This action is blocked by low doses of pancuronium or tubocurarine.25 This phenomenon is felt to be a big factor in the onset of muscle weakness in the phase.

Lab Parameters

Inhibition of cholinesterase activity

The definitive and the gold standard method in the diagnosis of OPC poisoning is established by demonstrating a decreased cholinesterase in the blood[19, 20].Theoretically, RBC or true cholinesterase is a more accurate test compared to serum or butyryl or pseudo cholinesterase; but the serum cholinesterase (SChE) is more readily available and measured in most labs, easier to assay and more useful in acute exposure. Ideally, the diagnosis of OPC poisoning is based on a drop of 50% of normal value of cholinesterase from the baseline. Since most patients don't have baseline values, the diagnosis can be confirmed by a progressive increase in cholinesterase value with treatment. Mild poisoning is defined as cholinesterase of 20-50%, moderate 10-20% and severe<10% of normal enzymatic activity. It is to be noted that unfortunately many labs don't have the in-house capability to run the cholinesterase levels. So it is important that any patient presenting with Full-blown cholinergic syndrome should be treated empirically without waiting for the lab confirmation of decreased cholinesterase activity.[21]

Another important use of cholinesterase (serum) is in the monitoring the clinical course of the patients with the poisoning.

Most chemical sufferers get this standard battery of tests and are told there is nothing wrong with the Antibodies to brain proteins (cytoskeleton antibodies) sometimes raised (test not available in UK).

MANAGEMENT

Before managing the case, it is vital to protect yourself with universal methods of precaution. Initial assessment involves checking airway, breathing and circulation. As part of this process, provide high-flow oxygen if available Extension of the neck helps to keep the airway patent. Airway should be secured with proper positioning and if necessary Guedel airway and endotracheal intubation should done. Place the patient in the left lateral position, ideally in a head-down position, to reduce the risk of aspiration.

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. If available, affix a pulse oximeter. Frequent suctioning is essential as excessive oropharyngeal and respiratory secretions may occlude the airway.The clothes should be removed as frequently contaminated with poison and vomiting. Skin vigorously washed with soap and water. Gastric lavage may help to reduce the absorption of the ingested poison and should be considered in patients within 1-2 hours.

Next, assess whether the patient requires atropine. Five routine assessments are crucial : miosis, excessive sweating, poor air entry into the lungs, bradycardia, and hypotension .Severely OP- or carbamate-poisoned patients are typically covered with sweat, and have small pinpoint pupils and laboured breathing (often with marked bronchorrhoea and wheeze). The presence of pinpoint pupils and excessive sweat suggests that the patient has taken an OP or carbamate and requires atropine. The heart rate may be slowed, but normal or even fast heart rates are common.

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.

If none of these signs are present, then the patient does not yet have clinical cholinergic poisoning and does not require atropine. However, it is possible that these signs will occur later, for example as a pro-poison (thion) OP is converted to the active oxon form, as a fat-soluble OP such as fenthion leaches out of fat stores into the

blood, or if the patient has presented soon after the ingestion. Careful observation is required to look for the development of cholinergic signs.

Atropine. Atropine has been the cornerstone in the management of OP poisoning for decades and will remain same for long Time. It acts competitively at the peripheral and central muscarinic receptors and antagonizes the parasympathetic effects of excess ACh at these sites. It reverses life threatening features of poisoning. Delay or in adequate atropine can result in death from central respiratory depression, bronchospasm, severe bradycardia and hypotenrtion

It is the physiological antidote for acetylcholine and blocks it at muscarinic and not nicotinic receptors. The onset of

action is within 1-4 minutes and peak effect is in 8 minutes. Out of the various signs of atropinization, the target endpoints for atropine therapy are –

1. Drying of pulmonary secretions with no wheeze,
2. Heart rate>80/min,
3. Pupil no longer pinpoint,
4. Dry axilla,
5. Systolic BP>80mmhg.

The drying of pulmonary secretions is the most important and most reliable endpoint and not tachycardia or mydriasis.

Atropine is given as 1-2 mg IV (children0.05mg/kg) and if there is no effect, the dose is doubled every 5-10 minutes. In massive exposure, large doses (300-1500mgs/day) of atropine may be needed by continuous IV infusion. When the patient achieves most of (at least 4 out of 5) the target therapy I.e. fully atropinized, an intravenous infusion is set up to maintain the therapeutic effect of atropine .Dose of atropine is kept 20% of initial atomization dose over hour .This dose is continued for initial 48 hours and gradually taper over 5-10 days. During this period adequacy of treatment is monitored very strictly patient is seen at least hourly for the next 6 hours to check the effectiveness of atropine infusion.[22,23] Studies have found that continuous atropine infusion is more effective than Intermittent boluses in decreasing respiratory failure and mortality As the required dose of atropine falls, the observation for recurrence of cholinergic features can be done less often (every 2-3hrs). Monitoring during atropine therapy can be done as shown in this tabular column given below [24,]

The markers used to detect atropine toxicity are – confusion, pyrexia, absent bowel sounds and urinary retention. The most common cause of respiratory failure and mortality in the early period of poisoning (usually < 48 hours) is inadequate atropinization. Another cholinergic agent, which is used in some centers: Glycopyrrolate- (Dose-0.05mg/kg) the main advantages of glycopyrrolate over atropine are -nil central toxicity (centralantichoilinergic syndrome) as it is a quaternary ammonium compound and hence has no CNS penetration and better control of tracheobronchial secretions

0XIMES:

These agents reactivate acetyl cholinesterase by removing the phosphoryl group. Amongst the various oximes like, obidoxime, diacetyl monoxime, and bisaldoxime, pralidoxime (2-PAM or P2AM –2hydroxy iminomethyl-1-methyl pyridinium chloride) is most often used, world wide. They prevent continued toxicity by scavenging (direct reaction and detoxification) the remaining organ phosphorous (OP) molecule. They also have anendogenous anticholinergic effect in normal doses. Their major effects are on the peripheral nervous system (PNS), where they reverse the cholinergic nicotinic effects like muscle weakness and

fasciculation and hence aid in recovery of neuromuscular transmission. It prevents the development of IMS, when started early and also helps in rapid recovery in patients on ventilator due to IMS. Since its lipid solubility is low, it has limited CNS penetration and activity.

The therapeutic effectiveness (window)of oximes depends upon **–**

1. Concentration of poison consumed (poison load),
2. Time elapsing between poisoning and oxime Administration,
3. Type of the OPC consumed -oximes have greater effect on diethyl compounds (parathion, diazinon) than dimethyl compounds (malathion, methyl dematin). [36] This is dueto the fact that diethyl compounds reactivate and “age” at a significantly slower rate than dimethyl compounds,

4. Concentration of oximes in the blood,

5. Release of OPC from lipid stores over a prolonged time. OPC is not a single entity, with sublential with variability in clinical course, response to oximes and outcome[18].

The clinical benefit of oximes for OP pesticide poisoning is not clear, being limited by the type of OP, poison load, time to start of therapy, and dose of oxime. 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. Where obidoxime is available, a loading dose of 250 mg is followed by an infusion giving 750 mg every 24 hours. Too rapid administration will result in vomiting, tachycardia and hypertension (especially diastolic hypertension).

Review the patient and assess the five parameters every 15 min or so to see whether the atropine infusion rate is adequate. As atropinisation is lost, with for example recurrence of bronchospasm or bradycardia, give further boluses of atropine until they disappear, and increase the infusion rate

Once the parameters have settled, see the patient at least hourly for the first 6 hours to check that the atropine infusion rate is sufficient and that there are no signs of atropine toxicity. As the required dose of atropine falls, observation for recurrence of cholinergic features can be done less often (every 2–3 hours). However, regular observation is still required to spot patients at risk of, and going into, respiratory failure.

Observation for impending respiratory failure and recurring cholinergic crises

Watch for early signs of intermediate syndrome in OP-poisoned patients. Weakness of neck flexion is common: the patient has difficulty lifting their head off the pillow; subsequent signs include the use of accessory muscles of respiration, nasal flaring, tachypnoea, sweating, cranial nerve palsies and proximal muscle weakness in the limbs with retained distal muscle strength.

Not all patients with neck weakness will develop the full intermediate syndrome requiring intubation and ventilation, but such patients are at risk and should be seen regularly. Measure tidal or minute volume and blood gases, if available. A locally agreed value should act as a trigger for prophylactic sedation and intubation, followed as necessary by ventilation.

Recurrence of toxicity, requiring atropine therapy, commonly occurs after poisoning with fat-soluble OPs, such as fenthion, that leak out of fat over days and even weeks. Recurring cholinergic crises may occur with little notice

Excess atropine causes agitation, confusion, urinary retention, hyperthermia, bowel ileus and tachycardia]. During regular observation for signs of overtreatment, check for the features given 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. The patient should then be seen frequently to ensure that the new infusion rate has reduced the signs of atropine toxicity without permitting the reappearance of cholinergic signs.

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CONCLUSION

Medical management of severe cholinergic pesticide poisoning is difficult, with high mortality. Some patients will die no matter how well managed. However, careful resuscitation with appropriate use of antidotes, followed by good supportive care and observation, should minimise the number of deaths in the period after admission to hospital.

Key messages

- Initial treatment of OP/carbamate pesticide poisoned patients involves the standard ABC of resuscitation.

- Since most deaths occur from respiratory failure, airway protection and ventilatory support is essential.
- Atropine can be given in an individualised dosing regimen to stabilise the patient.
- Careful observation probably saves many lives.

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