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Management of Organophosphorus Poisoning

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ABSTRACT

Organophosphorus (OP) compounds are widely used for agriculture, domestic pest-control and chemical warfare. Pesticide self-poisoning accounts for one-sixth to one-eighth of the world's suicides and a third of suicide deaths in rural Asia each year. OP pesticides inhibit cholinesterase enzymes leading to overstimulation of cholinergic receptors. Clinical features depend on the types of receptors stimulated at various sites of the body. The diagnosis of OP poisoning is made on the basis of history of poisoning, smell of pesticides, the characteristic clinical signs and reduced cholinesterase activity. Measurement of plasma cholinesterase is useful for diagnosis of OP poisoning although it may not directly correlate with severity of the poisoning. Atropine remains the main stay of treatment of OP poisoning with clear evidence of benefit if administered effectively. Atropine therapy should be monitored to maintain systolic blood pressure > 80 mmHg, pulse > 80 beats/min and clear chest on auscultation. Oximes reactivate cholinesterase enzymes and help to overcome even the nicotinic effects of OP poisoning. However, evidence for its effectiveness after self-poisoning is weak. Although several newer adjuvant therapies are tried to achieve better outcome, their potential benefits are not yet established.

Keywords: Cholinesterase management; organophosphorus poisoning.

INTRODUCTION

Organophosphorus (OP) compounds are widely used for agriculture, domestic pest-control and chemical warfare.[1] An estimated 25 million farmers from developing countries suffer from acute pesticide poisoning annually.[2] Pesticide self-poisoning accounts for one-six to one-eighth of the world's suicides and about 60% of the deaths from pesticide self-poisoning in rural Asia each year.[3-5]

Hospital based studies in Nepal revealed OP compounds as the most common poisoning agent comprising 52% of total cases.[6] Use of OP pesticides is widespread in Nepal, mainly in agricultural region. The OP compounds hold a major share of in-patient deaths among poisoning cases admitted in Nepalese hospitals[7-9] and methyl parathion is the most commonly consumed OP compound.[10,11]

The treatment outcome depends upon efficient intensive care and use of antidotes.[12] Atropine remains the main stay of treatment with weak evidence of benefit by oximes. Availability of standard treatment protocol in the hospital is a key to reduce the case fatality from OP poisoning.[13,14]

CLINICAL FEATURES

Organophosphorous (OP) pesticides inhibit cholinesterase enzymes irreversibly,[15] especially acetylcholinesterase (AChE) in synapses and on red-cell membranes, and butyrylcholinesterase (BuChE) in plasma. This leads to accumulation of acetylcholine and subsequent stimulation of cholinergic receptors at the neuromuscular junctions and in the autonomic and central nervous systems. Clinical features of OP pesticide poisonings depend on the types of cholinergic receptors stimulated at various sites in the body (Table 1).

Intermediate syndrome (IMS) is a distinct clinical entity

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Table 1. Clinical features of organophosphorus poisonings[16-18]

Muscarinic receptors in parasympathetic system	Nicotinic receptors in sympathetic system	Nicotinic and Muscarinic receptors in CNS	Nicotinic receptors at neuromuscular junction
• Bronchospasm • Bronchorrhoea • Miosis • Lacrimation • Urination • Diarrhoea • Hypotension • Bradycardia • Vomiting • Salivation	• Tachycardia • Mydriasis • Hypertension • Sweating	• Confusion • Agitation • Coma • Respiratory failure	• Muscle weakness • Paralysis • Fasciculation

occurring 24-96 h after exposure in 10-40% OP poisoning. This syndrome is characterized by neurological findings including weakness of neck flexion, proximal muscle and muscle of respiration, decreased deep tendon reflexes and cranial nerve abnormalities.[19] The exact mechanism of IMS is not known. Varying susceptibilities of various cholinergic receptors, prolonged AChE inhibition, inadequate oxime therapy, down regulation or desensitization of postsynaptic acetylcholine release, muscle necrosis and oxidative stress-related myopathy.[20]

DIAGNOSIS

The diagnosis of OP poisoning is made on the basis of clinical suspicion, the characteristic clinical signs (Table 1) and smell of pesticides or solvents. It should ideally be confirmed with an assay to measure BuChE activity in plasma (or AChE in whole blood).[21] Red cell AChE assays measure AChE expressed on the surface of red cells. It is a good marker of such inhibition in synapses and of poisoning severity. This enzyme is measured in whole blood in which BuChE activity has been blocked by an inhibitor. AChE is present at very low levels in human plasma and serum.[22] Moreover, the regeneration of AChE is slower than that of BuChE and the rate of spontaneous neuronal anticholinesterase recovery is unclear. Hence, BuChE assays can be relied upon to confirm exposure to an organophosphorus or carbamate pesticide. However, inhibition of BuChE does not give information about clinical severity of the poisoning. Many OP pesticides are more potent inhibitors of BuChE than they are of AChE; BuChE inhibition might occur to a greater extent than AChE inhibition.[23]

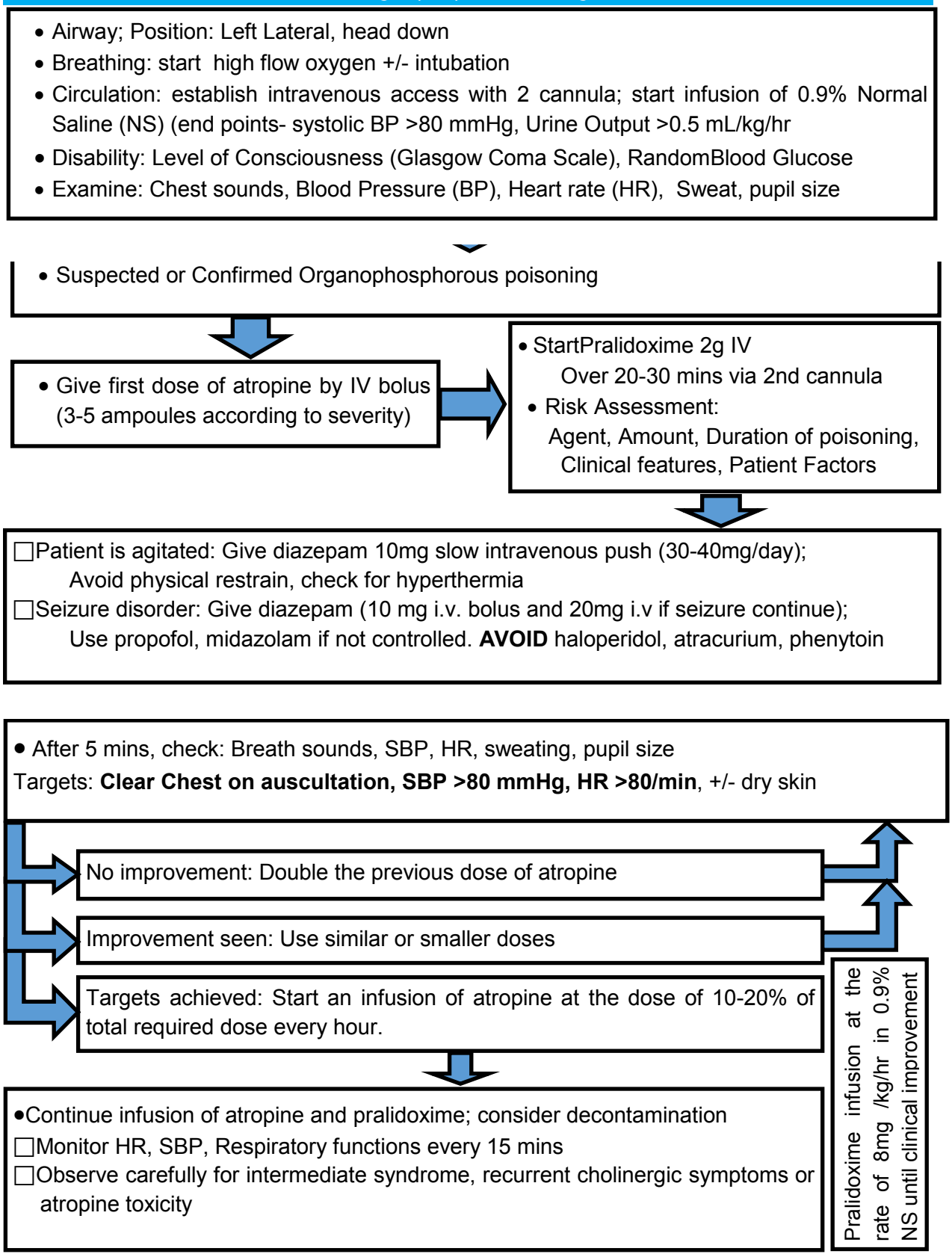
In addition, monitoring of BuChE does have a prognostic value. BuChE is produced by liver, and blood concentrations recover by about 7% of normal each day once the OP compound has been eliminated.[24] Daily BuChE assays can be used to monitor when enzyme activity starts to rise again, since this recovery suggests that the OP has been eliminated. It would also facilitate the decision to stop the treatment with oximes rationally. Control of temperature and pH are important for cholinesterase assays. The BuChE activity increases by 4% per 1°C increase in temperature.[25]

TREATMENT

Initial resuscitation to maintain airway, breathing and circulation, followed by administration of atropine and oxygen are considered to be the mainstays of treatment. An AChE reactivator (an oxime that reactivate AChE by removal of phosphate group) is also used despite their effectiveness being much debated.[26-28]

Resuscitation and stabilization of the patient should be accorded the first priority. Gastric decontamination should be considered only after this and for the cases that have taken large quantity of pesticides presenting

Chart 1. Guidelines for Treatment of Acute Organophosphorus Poisoning.[30,31]



Box1. Monitoring treatment with atropine.[30,31]

Insufficient atropine:

- Cholinergic features will re-emerge
- Atropinise the patient again with optimal atropine dose

During Atropinization:

- Tachycardia: could be due to nicotinic effects of poison, hypoxia, hypovolemia, alcohol withdrawal, or atropine itself; rapid administration of oximes. Continue doubling of dose
- Focal areas of crepitation: could be due to aspiration, atropinisation should not be continuedfor focal areas of crepitation
- Target (SBP, HR and clear chest) achieved, but pupils constricted: stop atropinisation
- Clear Chest, end points for SBP and HR not achieved (near end point achieved): Clinical judgement required, more atropine probably not required; consider using vasopressors
- Pupil very much dilated: Consider Atropine toxicity

Over atropinisation (Atropine Toxicity):

- Includes agitation, confusion, pyrexia, absent peristalsis, urinary retention, tachycardia
- Stop atropine, wait for 30-60 minutes (till symptoms subside) then continue atropine at 70-80% of previous infusion rate
- Control pyrexia with active cooling (fan, cold water sponging) to avoid hyperthermia induced cardiac arrest

Tapering Atropine:

- It is done on the basis of clinical response.
- Taper by 20% of the current dose at each stage

Intermediate Syndrome:

- Assess flexor neck strength regularly in conscious patients by asking them to lift their head off the bed and hold it in that position while pressure is applied to their forehead. Any sign of weakness is a sign that the patient is at risk of developing peripheral respiratory failure.
- 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.
- Tidal volume should be checked every 4 hr in such patients. Values less than 5 mL/kg indicate a need for intubation and ventilation

Recurrent Cholinergic crisis:

- Due to release of fat soluble OP pesticides from fat stores, may occur for several days to weeks after ingestion of someOP compounds such as fenthion
- Requiresretreatment with atropine and oximes.

within 1-2 hours of ingestion.[29] Patients must be carefully observed after stabilization for changes in

atropine needs, worsening respiratory function due to intermediate syndrome and recurrent cholinergic features occurring with fat soluble OP compounds. The current guidelines for treatment of acute OP poisoning are given in the Chart1 and Box1.

ATROPINE

Atropine remains the mainstay of therapy for the management of acute OP poisoning. It acts competitively at the peripheral and central muscarinic receptors and antagonizes the parasympathetic effects of excess acetylcholine at these sites. Sufficient atropine to stabilize the person should be given rapidly through continuous intravenous infusion.

DOSAGE AND ADMINISTRATION

The optimum dose of atropine has not been determined.[32] It varies among poisoned people because of variation in the dose and particular OP compound taken and possibly because of co-administration of an oxime (oximes have been proposed to have anticholinergic action at high doses).[33] It's worth considering that being too gentle by using dose of atropine less than 0.6 mg may paradoxically worsen the condition by producing bradycardia due to activation of M_1autoreceptors which are more sensitive to acetylcholine than M_2 receptors.[34]

Treatment is given according to the above mentioned guidelines with doubling doses in every 5 minutes with the aim to attain target end-points for atropine therapy by evaluating the improvement in cardiovascular function (systolic blood pressure >80 mmHg, pulse

rate>80 bpm) and respiratory function (no bronchorrhoea and bronchospasm). The regimen will allow for as much as 70 mg of atropine to be given in stages to a patient in less than 30 min, resulting in rapid stabilization and low risk of atropine toxicity. Once the patient achieves most of the target end-points for atropine therapy i.e. 'fully atropinised', an intravenous infusion is set up to maintain the therapeutics effects of atropine. There are different approaches of atropine infusion, the guidelines suggest an infusion giving every hour about 20% of the total dose needed to initially stabilize the patient and to continue this for first 48 hours before gradually tapering over hours and days.

The main adverse effects of too high an atropine dose are delirium, agitation, hyperthermia, absent bowel sounds and urinary retention.[35] If this happens, stop the infusion and wait for 30-60 min for these features to settle before starting again at 70-80% of previous infusion rate.

OXIMES

Oximes (such as pralidoxime, obidoxime, and HI-6) reactivate AChE inhibited by OP poisoning.Reactivation is limited by ageing of the ACh E and high concentrations of pesticides. Ageing of ACh E takes longer with diethyl OP compounds than with dimethyl OP compounds. In theory, oximes may be effective if started within about 120 hours for diethyl OP poisoning and 12 hours for dimethyl OP poisoning. Treatment may be beneficial if continued for as long as the person is symptomatic because it may take several days for the pesticide concentration to drop below the point at which the rate of reactivation surpasses reinhibition.[36]

There is currently mixed evidence regarding the clinical effectiveness of oximes and some OP pesticides do not respond well to oximes. However, until the evidence base for oximes becomes clearer, it is difficult to contradict the World Health Organization (WHO) guidelines to give high doses of oxime (pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hourfor the first two days) to all people with OP poisoning, especially in patients with nicotinic effects.[37] Adverse effects of oximes include hypertension, cardiac dysrhythmias (including cardiac arrest after rapid administration), headache, blurred vision, dizziness, and epigastric discomfort. Such adverse effects with pralidoxime have been reported only with either rapid administration or doses >30 mg/kg bolus. It may be difficult to distinguish these adverse effects from the effects of organophosphorus.[38] The infusion can be tapered after 2 days and restarted if there is clinical deterioration with withdrawal of oximes.However, according to a recent study,doses of PAM guided by the patients severity instead of strictly following WHO guidelines improve the outcomes of OP poisoning patients.[39]

BENZODIAZEPINES

Benzodiazepines are the first-line drugs for emergency control of seizures and agitation.[40] They bind to gamma-aminobutyric acid (GABA)-A receptors, increasing channel opening frequency at the receptor, with subsequent increase in chloride conductance and neuronal hyperpolarization, leading to enhanced inhibitory neurotransmission and antiepileptic action.[41] Routine use of benzodiazepine was supportive in animal model with OP poisoning but conclusive studies in human are lacking.[42] Patients poisoned with OP pesticides frequently become agitated. The cause is complex, with contributions from the pesticide itself, anxiety, atropine toxicity, hypoxia, alcohol ingested with the poison, and medical complications. Diazepam, lorazepam and midazolam are preferred benzodiazepines to treat seizure or agitation due to OP poisoning or due to drugs used for its treatment.[43] Diazepam at the dose of 10 mg given by slow IV push reduces agitation and can be repeated as necessary in an adultup to 30-40 mg per 24 hours.[31]

GASTROINTESTINAL DECONTAMINATION

Gastric lavage is often the first intervention done to poisoned patients at hospitals although no evidence shows any form of gastric decontamination to significantly benefit patients poisoned with OP pesticides (or other poisons).[44] Gastric lavage may delay administration of activated charcoal and specific treatment for OP poisoning. Gastric decontamination should only be done after the patient has been stabilized and treated with oxygen, atropine, and an oxime.[45] In patients who have taken a large amount of pesticide and are seen within 1 to 2 hours, consensus is that a single dose of activated charcoal after gastric lavage (using an NG tube and careful administration of small volumes of water) may offer benefit. It should be done in people who consent to this treatment or are unconscious and have had their airway protected.

NEWER THERAPIES

Various forms of therapeutic interventions including newer drugs, fresh frozen plasma and paraoxonases have been tried for management of OP poisoning with the hope of better outcome but results are still inconclusive due to the lack of sufficient data and randomized control trials.[46] Due to ethical ground, these therapies should not

be independently evaluated against the placebo so they had been evaluated as adjuvant to standard therapy.

MAGNESIUM SULPHATE

Magnesium sulphate is an inhibitor of acetylcholine release in the central nervous system and at peripheral sympathetic and parasympathetic synapses.[47] The administration of magnesium to animals poisoned with OP pesticides improves outcome, possibly owing to a favourable effects on neuromuscular junction block or increased hydrolysis of some pesticides.[48] The use of magnesium in acute OP poisoning in humans has been reported in three small studies. In the first study, intravenous administration of magnesium sulphate produced some improvement in neuromuscular function.[49] The second and third studies reported that magnesium decreased mortality compared with usual care.[50]

CLONIDINE

It is an α_2 adrenergic receptor agonist that reduces acetylcholine synthesis and release from pre-synaptic nerve terminals. It showed beneficial effect in animals when combined with atropine, but effects in human beings are unknown.[51]

SODIUM BICARBONATE

Studies in animals revealed that increasing blood pH in non-acidotic mice reduced mortality from OP poisoning.[52] Although human studies also claimed to have good results with sodium bicarbonate, those studies are not randomized control studies and there is nosufficient evidence for generalizing the observation.[53,54]

In addition, there have been studies with possible benefit following administration of fresh frozen plasma (FFP)[55],an OP hydrolase like paraoxonase that cleavesOP compounds[56], and antioxidants to prevent neuronal damage due to oxidative stress in acute OP poisoning.[57]

CONCLUSIONS

OP pesticide poisoning has been assumed major global health challenges and it is the most common poisoning associated with morbidity and mortality. Measurement of plasma cholinesterase is useful to retrospectively diagnose the poisoning although it may not directly correlate with the severity of the poison. Hence, resultof plasma cholinesterase should not be awaited to initiate therapy of suspected OP poisoning. Atropine remains the main stay of treatment of OP poisoning. Systolic blood pressure, pulse rate and chest auscultation are vital for monitoring the atropine therapy. Mixed evidence exists about benefit of oximes, with them being ineffective after ageing has occurred. Several newer adjuvant therapies with potential benefit have emerged. Further evidence has to be backed up by newer researchesfor establishing their role to bring about better outcome in OP poisoning.

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